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RIORDAN & HORGAN
523 Octavia Street
San Francisco, CA 94102
Telephone: (415) 431-3472

Attorneys for Defendant
BARRY LAMAR BONDS

FILED
FEB - 3 2009
RICHARD W. WIEKING
CLERK, U.S. DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

**UNITED STATES DISTRICT COURT**

**NORTHERN DISTRICT OF CALIFORNIA**

**SAN FRANCISCO DIVISION**

| | |
|---|---|
| UNITED STATES OF AMERICA, Plaintiff, vs. BARRY LAMAR BONDS, Defendant. | Case No. CR 07 0732 SI<br>Date: February 5, 2009<br>Time: 10:30 a.m.<br>Judge: The Honorable Susan Illston |

**EXHIBITS IN SUPPORT OF DEFENDANT'S REPLY TO UNITED STATES' OPPOSITION TO MOTION IN LIMINE TO EXCLUDE EVIDENCE**

[redacted]

# EXHIBIT A

GRAND JURY 04-1

NORTHERN DISTRICT OF CALIFORNIA

ORIGINAL

GJ INVESTIGATION NO. 2004R00608

REPORTER'S TRANSCRIPT OF PROCEEDINGS

TESTIMONY OF JAMES VALENTE

AT 450 GOLDEN GATE AVENUE

SAN FRANCISCO, CALIFORNIA 94102

THURSDAY, MAY 25, 2006

FOR THE GOVERNMENT:
KEVIN V. RYAN,
UNITED STATES ATTORNEY
BY: JEFF NEDROW, AUSA
MATT PARRELLA, AUSA
JEFF FINIGAN, AUSA
UNITED STATES DEPARTMENT OF JUSTICE
450 GOLDEN GATE AVENUE
SAN FRANCISCO, CALIFORNIA 94102

Q. Okay. And what would you do with the actual faxed reports that you received?
A. I created like files for the athletes or whoever it was testing.
Q. And what was your normal practice in terms of did you typically maintain those reports or did you toss them or shred them? What would you do with them?
A. No, we just kept them in their files.
Q. Okay. With respect to your interaction with Greg Anderson and Mr. Bonds, would you give them copies or talk to them about what the result said?
A. I didn't talk about the results, but I did give Greg copies.
Q. Okay. And I guess maybe now is the time since he's came up. Who was -- was Greg Anderson an employee at BALCO or who was he...
A. No.
Q. ...in connection with? No?
A. He was a personal trainer at the gym that was around the block from our office.
Q. Do you recall the name of the gym?
A. One time it was World's and then they changed it to -- I don't know. They changed it

Q. Okay. Okay. All right. Let's move on. And, again, this is the kind of thing you would have kept in Mr. Bonds' folder as a part of your records; correct?

A. Yes.

Q. Okay. Great.

ASST. FOREPERSON: Can I ask a question...

MR. NEDROW: Sure.

ASST. FOREPERSON: ...'cause I don't think it can wait.

MR. NEDROW: Okay.

ASST. FOREPERSON: Nobody witnessed the -- the collection of the urinalysis. So if the urinalysis was from a female, would the testosterone level come out to be zero?

MR. NEDROW: If -- if you know the answer.

THE WITNESS: I don't know. It could, I guess. Yeah, there was no chain of custody on the urine. I was just being -- they would send it in with their names on -- on it or I would be given it, given to at the time and then, you know, like Greg would tell me it was Barry's urine.

Q. BY MR. NEDROW: Okay. Well, I do want to follow up, thank you, to be clear on that, that when you say there's no chain of custody, you're referring specifically to formal documents that -- you know, affidavits and things; correct?

A. Yes. Correct.

Q. All right. But, of course, when you do that, that creates a paper trail; correct?

A. Yes.

Q. Okay. All right. So what was your basis for putting down Barry B. and these numbers on these samples? I mean how did you know it was Barry's urine?

A. 'Cause Greg gave it to me and told me.

Q. Greg told you specifically these were Barry's urine samples.

A. Yes.

Q. Okay. All right. Let's go to the next --

GRAND JUROR: Mr. Nedrow.

MR. NEDROW: Yes. I'm sorry.

GRAND JUROR: Can we request a bathroom break?

MR. NEDROW: Oh, sure. Yeah. Absolutely. You guys want to take like 10 minutes or something or --

GRAND JUROR: Five is fine.

GRAND JUROR: Yeah, five is fine.

THE FOREPERSON: Five is fine.

analysis...

Q. Okay.

A. ...or the element analysis.

Q. Okay. And we have a date, of course. Who's listed as the consulting physician for Mr. Bonds in the first line?

A. "Dr. Goldman."

Q. And just tell us briefly who Dr. Goldman was in connection with BALCO.

A. He was the medical director. He oversaw the operations at BALCO.

Q. Okay. And was he actually someone who came to BALCO and got involved in dealing with the -- the medical issues at BALCO?

A. Yes.

Q. Okay. Did you ever hear or see him consulting with Mr. Bonds?

A. No.

Q. Okay. All right. And then when we go to the next few pages -- now, there's a different lab indicated starting on page 26. This is something called "Specialty Laboratories." Do you see that?

A. Yes.

Q. How is that different from Quest Diagnostics? Can you explain how this is used

A. Yeah, he just asked. He said, "Do me a favor. Can you switch my name for Barry's?" and I said, "If that's what you want to do" and he said, "Yeah" and I said, "Okay."

Q. And -- and just so we're clear, I guess what you said earlier, was there a concern stated by Mr. Anderson that Mr. Bonds wanted some privacy or was concerned about it for some reason?

A. Yes. He just said -- he said Barry wanted, you know, some privacy, so he didn't want his name on it.

Q. So did that suggest to you that Mr. Bonds was aware this was happening...

A. I believe so, yes.

Q. ...based on what Mr. Anderson said?

A. Yes.

Q. But did you personally talk to Mr. Bonds about this particular incident?

A. No.

Q. And I guess I see the grand juror's concern, I mean in the question. This in theory I guess would allow the identity of samples to be handled without the submitting person's knowledge. I mean isn't that true?

A. Yes.

STATE OF CALIFORNIA )
) ss
COUNTY OF SAN MATEO )

I hereby certify that the foregoing in the within-entitled cause was taken at the time and place herein named; that the transcript is a true record of the proceedings as reported by me, a duly certified shorthand reporter and a disinterested person, and was thereafter transcribed into typewriting by computer.

I further certify that I am not interested in the outcome of the said action, nor connected with, nor related to any of the parties in said action, nor to their respective counsel.

IN WITNESS WHEREOF, I have hereunto set my hand this 29th day of May, 2006.

Victoria Lee

VICTORIA LEE, CSR# 11547
STATE OF CALIFORNIA

# EXHIBIT B

BALCO
BAY AREA LABORATORY
CO-OPERATIVE

July 6, 2001

Dr. Victor Uralets
Quest Diagnostics Sports Testing
7470 Mission Valley Road
San Diego, CA 92108
(619) 686-3000

ID, 100321
Y2733161

Attention: Deliver this urine specimen to Dr. Victor Uralets

Dear Dr. Uralets:

As discussed, Dr. Goldman would like the sports panel performed for patient sample **100321** The **test code is #6015** for this sample. This is a **non forensic** sample.

The BALCO account # is 14059.

Enclosed is check #0794 in the amount of $80.00 per sample.

Please **fax the test result to (650) 697-6576 ASAP**.

Thanks

Sincerely,

Jim Valente

QD 000168

1520 Gilbreth Road • Burlingame, CA 94010 • (650) 697-6708 • 1-800-777-7122 • FAX (650) 697-6576 • www.balcolab.com

BB001069

BALCO
BAY AREA LABORATORY
CO-OPERATIVE

October 22, 2001

ID, 100404
CC
Y2893085
3880

Dr. Victor Uralets
Quest Diagnostics Sports Testing
7470 Mission Valley Road
San Diego, CA 92108
(619) 686-3000

Attention: Deliver these urine specimens to Dr. Victor Uralets

Dear Dr. Uralets:

As discussed, Dr. Goldman would like the sports panel performed for sample patient **100402**, patient sample **100403** and sample patient **100404**. The **test code is #6015** for these samples. These are **non forensic** samples.

The BALCO account # is 14059.

Enclosed is check #0850 in the amount of $240.00 ($80.00 per sample).

Please **fax the test result to (650) 697-6576 ASAP**.

Thanks

Sincerely,

Jim Valente

QD 000226

BALCO
BAY AREA LABORATORY
CO-OPERATIVE

February 6, 2003

Dr. Victor Uralets
Quest Diagnostics Sports Testing
7470 Mission Valley Road
San Diego, CA 92108
(619) 686-3000

Attention: Deliver these urine specimens to Dr. Victor Uralets

Dear Dr. Uralets:

As discussed, Dr. Goldman would like the sports panel performed for sample patient **100552** sample, patient **100553** and sample patient **100554**. The **test code is ~~#6015~~** for these samples. These are **non forensic** samples.

test code: 38289N

The BALCO account # is 41125218.

Enclosed is check # 1117 in the amount of $80.00 ($80.00 per sample).

Please **fax the test result to (650) 697-6576 ASAP**.

Thanks

AM
373270550574006
exp 05/03

Sincerely,

Jim Valente

Cathy Daikes

QD 000370

9009147

4230 South Burnham
~~Las Vegas, NV 89119~~

948757H

# BALCO
BAY AREA LABORATORY CO-OPERATIVE

May 30, 2003

Dr. Victor Uralets
Quest Diagnostics Sports Testing
7470 Mission Valley Road
San Diego, CA 92108
(619) 686-3000

Attention: Deliver these urine specimens to Dr. Victor Uralets

Dear Dr. Uralets:

As discussed, Dr. Goldman would like the sports panel performed for sample patient **100571** and sample patient **100572**. The **test code is #38289N** for these samples. These are **non forensic samples**.

The BALCO account # is 41125218.

Please **fax the test result to (650) 697-6576 ASAP**.

Thanks

Sincerely,

Jim Valente

06 02 03 Federal Express JEREMY SHUCK

Seal/Bag Intact
ID Verified

QD 000412

**000006**

# EXHIBIT C

SPECIALTY LABORATORIES
2211 Michigan Avenue 310-828-6543
Santa Monica, CA 90404-3900 800-421-4449

SPECIALTY# 098-6186805
CLIENT # 44008

NAME: B, B

PHYSICIAN: GOLDMAN, BRIAN H
NOTES:
PATIENT ID: 00216
SPECIMEN ID: 00216

BALCO LABS
ATTN: JIM VALENTE
1520 GILBREATH ROAD

BURLINGAME CA 94010

DOB: 07/24/64 AGE: 36 Years
SEX: Male

DRAWN: 01/19/01 15:00
RECEIVED: 01/22/01 17:09
PRINTED: 01/26/01 08:40
FINAL REPORT: 01/26/01 08:40
FINAL

| TEST NAME | RESULTS | | | REFERENCE RANGE |
|---|---|---|---|---|
| **TESTOSTERONE, FREE & TOTAL** | | | | |
| Testosterone Total | 730 | | ng/dL | (241-827) |
| Testosterone Free | > 5.00 | | ng/dL | |

REFERENCE RANGES for Testosterone Free
Males:
20-49 yrs . . . . . . 0.95-4.30 ng/dL
> 50 yrs . . . . . . 0.80-3.50 ng/dL
Females:
Ovulating . . . . Up to 0.38 ng/dL
Postmenopausal . . Up to 0.18 ng/dL

% Free Testosterone % of total (0.32-0.50)
The percentage of total testosterone in unbound state (% free testosterone) cannot be calculated since the free testosterone level is greater than the highest detectable concentration.

| COMPLETE BLOOD COUNT | | | | |
|---|---|---|---|---|
| WBC | 7.9 | | thou/cu mm | (4.0-11.0) |
| RBC | 5.34 | | mil/cu mm | (4.50-6.00) |
| Hgb | 14.0 | | g/dL | (13.5-18.0) |
| Hct | 44.9 | | % | (40.0-54.0) |
| MCV | 84 | | fL | (80-96) |
| MCH | 26 | | pg | (26-34) |
| MCHC | 31 | | g/dL | (31-37) |
| Platelets | 388 | | thou/cu mm | (150-400) |
| Segmented Neutrophils | 73 | H | % | (50-70) |
| Basophils | 0 | | % | (< 2) |
| Eosinophils | 3 | | % | (< 6) |
| Lymphocytes | 23 | | % | (20-40) |
| Monocytes | 0 | | % | (< 8) |
| RBC Morphology | Normal | | | |

F44008 19242 1
R10271 (1/97) Page 2

Albert Rabinovitch, MD, PhD

BB000145

SPECIALTY LABORATORIES
2211 Michigan Avenue 310-828-6543
Santa Monica, CA 90404-3900 800-421-4449

SPECIALTY# 098-6186805
CLIENT # 44008

NAME: B, B

PHYSICIAN: GOLDMAN, BRIAN H
NOTES:
PATIENT ID: 00216
SPECIMEN ID: 00216

BALCO LABS
ATTN: JIM VALENTE
1520 GILBREATH ROAD

BURLINGAME CA 94010

DOB: 07/24/64 AGE: 36 Years
SEX: Male

DRAWN: 01/19/01 15:00
RECEIVED: 01/22/01 17:09
PRINTED: 01/26/01 08:40
FINAL REPORT: 01/26/01 08:40
FINAL

| TEST NAME | RESULTS | | | REFERENCE RANGE |
|---|---|---|---|---|
| **AUTOANTIBODY CONFIRMATION [IB]** | | | | |
| U1 RNP/snRNP IgG Autoabs | Not detected | | | Not detected |
| Sm IgG Autoabs | Not detected | | | Not detected |
| Scl-70 IgG Autoabs | Not detected | | | Not detected |

This test result or one or more of its components was developed and its performance characteristics determined by Specialty Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

| TEST NAME | RESULTS | FLAG | UNITS | REFERENCE RANGE |
|---|---|---|---|---|
| **LACTATE DEHYDROGENASE** | | | | |
| Lactate Dehydrogenase (LDH) | 208 | | U/L | (< 251) |
| **CHOLESTEROL EVALUATION** | | | | |
| Triglycerides | 195 | | mg/dL | (< 200) |
| Cholesterol, Total | 178 | | mg/dL | (< 200) |
| HDL-C | < 20 | L | mg/dL | (> 34) |
| LDL-C (Calc) | < 132 | H | mg/dL | (< 130) |
| Cholesterol/HDL-C Ratio | > 25.43 | H | | (< 5.00) |

F44008 19242 1
R10271 (1/97) Page 3

Albert Rabinovitch, M.D.,Ph.D.

LabOne

1010… ..nner Boulevard
Lenexa, KS 66219-9752
(800) 646-7788
now a part of Quest Diagnostics

PATIENT: BONDS, BARRY
CLIENT PATIENT ID: ?
REQ NUMBER: 70146002-16
ID OR ROOM NO: UNKNOWN
PAGE DOB/AGE: Jul 24 1964/37 YEARS
1 SEX: M FASTING: YES HRS: 12
DATE/TIME COLL: Nov 08 2001 00:00
DATE RECEIVED: Nov 09 2001 06:50 AM
DATE REPORTED: Nov 13 2001
DATE RE-SENT: Nov 28 2006
REPORT STATUS: RESEND REPORT

ACCOUNT: J9R3
REF DR: UNKNOWN

BRIAN GOLDMAN, MD
1520 GILBRETH ROAD
BURLINGAME, CA 94010

| RESULT NAME | IN RANGE | OUT OF RANGE | REFERENCE | UNITS |
|---|---|---|---|---|
| BLOOD CHEMISTRY | | | | |
| NO HEMOLYSIS DETECTED | | | | |
| NO LIPEMIA DETECTED | | | | |
| NO ICTERUS DETECTED | | | | |
| SODIUM | 140 | | 136 - 146 | MEQ/L |
| POTASSIUM | 4.4 | | 3.6 - 5.1 | MEQ/L |
| CHLORIDE | 102 | | 98 - 109 | MEQ/L |
| GLUCOSE | 75 | | 60 - 109 | MG/DL |
| CALCIUM | 9.4 | | 8.5 - 10.5 | MG/DL |
| BUN | 20 | | 6 - 23 | MG/DL |
| CREATININE | | 1.6 | 0.3 - 1.5 | MG/DL |
| BUN/CREAT RATIO | 12.5 | | 10 - 22 | |
| TOTAL BILIRUBIN | 0.5 | | 0.2 - 1.3 | MG/DL |
| AST (SGOT) | | 67 | 10 - 45 | U/L |
| ALT (SGPT) | | 177 | 11 - 45 | U/L |
| ALKALINE PHOSPHATASE | 79 | | 40 - 115 | U/L |
| TOTAL PROTEIN | 7.5 | | 6.3 - 7.8 | G/DL |
| ALBUMIN | 4.3 | | 3.90 - 5.20 | G/DL |
| GLOBULIN | 3.2 | | 1.8 - 3.5 | G/DL |
| A/G RATIO | 1.3 | | 1 - 2.5 | |
| TRIGLYCERIDES | 102 | | 10 - 150 | MG/DL |
| CHOLESTEROL | | 222 | 140 - 199 | MG/DL |
| | BORDERLINE HIGH CHOL | | 200 - 239 | MG/DL |
| | HIGH CHOLESTEROL | | >= 240 | MG/DL |
| HDL CHOLESTEROL | 40 | | 27 - 75 | MG/DL |
| CHOL/HDL RATIO | | 5.6 | 0 - 5 | |
| LDL CHOLESTEROL, CALC | | 161 | 0 - 129 | MG/DL |
| VLDL, CALCULATED | 20 | | 5 - 35 | MG/DL |
| LDL/HDL RATIO | 4.04 | | 1.52 - 5.52 | |
| BICARBONATE | 26 | | 21 - 30 | MEQ/L |
| HEMATOLOGY | | | | |
| HGB | 15.4 | | 14.0 - 18.0 | G/DL |
| HCT | 46.4 | | 44.0 - 54.0 | % |
| RBC | 5.70 | | 4.70 - 6.10 | MILLION/MCL |
| MCV | | 81 | 83 - 103 | FL |
| MCH | 26.9 | | 26.0 - 35.0 | PG |
| MCHC | 33.2 | | 30.0 - 37.0 | G/DL |
| RDW | | 15.1 | 11.5 - 14.5 | % |
| WBC | 5.7 | | 4.0 - 11.0 | K/MCL |
| NEUTROPHILS | 48 | | 42 - 77 | % |
| LYMPHOCYTES | 43 | | 16 - 43 | % |
| MONOCYTES | 6 | | 4 - 12 | % |
| EOSINOPHILS | 3 | | 0 - 8 | % |
| BASOPHILS | 0 | | 0 - 3 | % |
| PLATELET COUNT | 231 | | 130 - 400 | K/MCL |

- REPORT CONTINUED ON NEXT PAGE -

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LabOne
10101 ...ner Boulevard
Lenexa, KS 66219-9752
(800) 646-7788
now a part of Quest Diagnostics

PATIENT: BONDS, BARRY
CLIENT PATIENT ID: ?
REQ NUMBER: 70145977-16
ID OR ROOM NO: UNKNOWN
PAGE DOB/AGE: Jul 24 1964/37 YEARS
1 SEX: M FASTING: YES HRS:
DATE/TIME COLL: Apr 12 2002 10:00 AM
DATE RECEIVED: Apr 15 2002 06:05 AM
DATE REPORTED: Apr 15 2002
DATE RE-SENT: Nov 28 2006
REPORT STATUS: RESEND REPORT

ACCOUNT: J9R3
REF DR: UNKNOWN

BRIAN GOLDMAN, MD
1520 GILBRETH ROAD
BURLINGAME, CA 94010

| RESULT NAME | IN RANGE | OUT OF RANGE | REFERENCE | UNITS |
|---|---|---|---|---|
| BLOOD CHEMISTRY | | | | |
| NO HEMOLYSIS DETECTED | | | | |
| NO LIPEMIA DETECTED | | | | |
| NO ICTERUS DETECTED | | | | |
| SODIUM | 139 | | 136 - 146 | MEQ/L |
| POTASSIUM | 4.1 | | 3.6 - 5.1 | MEQ/L |
| CHLORIDE | 105 | | 98 - 109 | MEQ/L |
| GLUCOSE | 104 | | 60 - 109 | MG/DL |
| CALCIUM | 9.1 | | 8.5 - 10.5 | MG/DL |
| BUN | | 26 | 6 - 23 | MG/DL |
| CREATININE | | 1.7 | 0.3 - 1.5 | MG/DL |
| BUN/CREAT RATIO | 15.3 | | 10 - 22 | |
| TOTAL BILIRUBIN | 0.3 | | 0.2 - 1.3 | MG/DL |
| AST (SGOT) | | 51 | 10 - 45 | U/L |
| ALT (SGPT) | | 57 | 11 - 45 | U/L |
| ALKALINE PHOSPHATASE | 84 | | 40 - 115 | U/L |
| TOTAL PROTEIN | 6.5 | | 6.3 - 7.8 | G/DL |
| ALBUMIN | | 3.8 | 3.90 - 5.20 | G/DL |
| GLOBULIN | 2.7 | | 1.8 - 3.5 | G/DL |
| A/G RATIO | 1.4 | | 1 - 2.5 | |
| BICARBONATE | 23 | | 21 - 30 | MEQ/L |
| HEMATOLOGY | | | | |
| HGB | 14.6 | | 14.0 - 18.0 | G/DL |
| HCT | 49.1 | | 44.0 - 54.0 | % |
| RBC | 5.40 | | 4.70 - 6.10 | MILLION/MCL |
| MCV | 91 | | 83 - 103 | FL |
| MCH | 27.1 | | 26.0 - 35.0 | PG |
| MCHC | | 29.7 | 30.0 - 37.0 | G/DL |
| RDW | | 16.4 | 11.5 - 14.5 | % |
| WBC | 7.6 | | 4.0 - 11.0 | K/MCL |
| NEUTROPHILS | 60 | | 42 - 77 | % |
| LYMPHOCYTES | 36 | | 16 - 43 | % |
| MONOCYTES | | 3 | 4 - 12 | % |
| EOSINOPHILS | 1 | | 0 - 8 | % |
| BASOPHILS | 1 | | 0 - 3 | % |
| PLATELET COUNT | 239 | | 130 - 400 | K/MCL |

REMARKS: RESULTS MAY BE AFFECTED BY SPECIMEN AGE.

END OF REPORT FOR BONDS, BARRY

CONFIDENTIAL

LabOne
1010 .nner Boulevard
Lenexa, KS 66219-9752
(800) 646-7788
now a part of Quest Diagnostics

PATIENT: BONDS, BARRY
CLIENT PATIENT ID: ?
REQ NUMBER: 70146002-16
ID OR ROOM NO: UNKNOWN
PAGE 1
DOB/AGE: Jul 24 1964/37 YEARS
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DATE RE-SENT: Nov 28 2006
REPORT STATUS: RESEND REPORT

ACCOUNT: J9R3
REF DR: UNKNOWN

BRIAN GOLDMAN, MD
1520 GILBRETH ROAD
BURLINGAME, CA 94010

| RESULT NAME | IN RANGE | OUT OF RANGE | REFERENCE | UNITS |
|---|---|---|---|---|
| BLOOD CHEMISTRY | | | | |
| NO HEMOLYSIS DETECTED | | | | |
| NO LIPEMIA DETECTED | | | | |
| NO ICTERUS DETECTED | | | | |
| SODIUM | 140 | | 136 - 146 | MEQ/L |
| POTASSIUM | 4.4 | | 3.6 - 5.1 | MEQ/L |
| CHLORIDE | 102 | | 98 - 109 | MEQ/L |
| GLUCOSE | 75 | | 60 - 109 | MG/DL |
| CALCIUM | 9.4 | | 8.5 - 10.5 | MG/DL |
| BUN | 20 | | 6 - 23 | MG/DL |
| CREATININE | | 1.6 | 0.3 - 1.5 | MG/DL |
| BUN/CREAT RATIO | 12.5 | | 10 - 22 | |
| TOTAL BILIRUBIN | 0.5 | | 0.2 - 1.3 | MG/DL |
| AST (SGOT) | | 67 | 10 - 45 | U/L |
| ALT (SGPT) | | 177 | 11 - 45 | U/L |
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| | | BORDERLINE HIGH CHOL | 200 - 239 | MG/DL |
| | | HIGH CHOLESTEROL | >= 240 | MG/DL |
| HDL CHOLESTEROL | 40 | | 27 - 75 | MG/DL |
| CHOL/HDL RATIO | | 5.6 | 0 - 5 | |
| LDL CHOLESTEROL, CALC | | 161 | 0 - 129 | MG/DL |
| VLDL, CALCULATED | 20 | | 5 - 35 | MG/DL |
| LDL/HDL RATIO | 4.04 | | 1.52 - 5.52 | |
| BICARBONATE | 26 | | 21 - 30 | MEQ/L |
| HEMATOLOGY | | | | |
| HGB | 15.4 | | 14.0 - 18.0 | G/DL |
| HCT | 46.4 | | 44.0 - 54.0 | % |
| RBC | 5.70 | | 4.70 - 6.10 | MILLION/MCL |
| MCV | | 81 | 83 - 103 | FL |
| MCH | 26.9 | | 26.0 - 35.0 | PG |
| MCHC | 33.2 | | 30.0 - 37.0 | G/DL |
| RDW | | 15.1 | 11.5 - 14.5 | % |
| WBC | 5.7 | | 4.0 - 11.0 | K/MCL |
| NEUTROPHILS | 48 | | 42 - 77 | % |
| LYMPHOCYTES | 43 | | 16 - 43 | % |
| MONOCYTES | 6 | | 4 - 12 | % |
| EOSINOPHILS | 3 | | 0 - 8 | % |
| BASOPHILS | 0 | | 0 - 3 | % |
| PLATELET COUNT | 231 | | 130 - 400 | K/MCL |

- REPORT CONTINUED ON NEXT PAGE -

CONFIDENTIAL

LabOne

1010 [illegible]nner Boulevard
Lenexa, KS 66219-9752
(800) 646-7788
now a part of Quest Diagnostics

PATIENT: BONDS, BARRY
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REQ NUMBER: 70146002-16
ID OR ROOM NO: UNKNOWN
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DOB/AGE: Jul 24 1964/37 YEARS
SEX: M FASTING: YES HRS: 12
DATE/TIME COLL: Nov 08 2001 00:00
DATE RECEIVED: Nov 09 2001 06:50 AM
DATE REPORTED: Nov 13 2001
DATE RE-SENT: Nov 28 2006
REPORT STATUS: RESEND REPORT

ACCOUNT: J9R3
REF DR: UNKNOWN

BRIAN GOLDMAN, MD
1520 GILBRETH ROAD
BURLINGAME, CA 94010

| RESULT NAME | IN RANGE | OUT OF RANGE | REFERENCE | UNITS |
|---|---|---|---|---|
| SEND OUT TESTS PERFORMED AT: QUEST DIAGNOSTICS AMD, 14225 NEWBROOK DRIVE, NICHOLS INSTITUTE, CHANTILLY, VA 20153 — 800-336-3718 | | | | |
| Free and Total Testosterone | | | | |
| Free and Total Testosterone | | | | |
| Free Testosterone | 11.2 | | 9.5-29.7 | pg/mL |
| Total Testosterone | 336 | | 240-980 | ng/dL |
| % Free Testosterone | 0.3 | | 0.2-0.7 | % |
| SEND OUT TESTS PERFORMED AT: ARUP LABORATORIES, 500 CHIPETA WAY, SALT LAKE CITY, UT 84108 — 800-522-2787 | | | | |
| IGF-1 (INSULIN-LIKE GROWTH I) FROZEN AT LABONE. | | | | |
| IGF-1 (INSULIN-LIKE GROWTH I) | | 100 | 114-492 | ng/mL |

REFERENCE INTERVAL: IGF-1 (Insulin-Like Growth I)

| AGE | MALE | FEMALE |
|---|---|---|
| 2 mos-5 yrs | 17-248 ng/mL | 17-248 ng/mL |
| 6-8 yrs | 88-474 ng/mL | 88-474 ng/mL |
| 9-11 yrs | 110-565 ng/mL | 117-771 ng/mL |
| 12-15 yrs | 202-957 ng/mL | 261-1096 ng/mL |
| 16-24 yrs | 182-780 ng/mL | 182-780 ng/mL |
| 25-39 yrs | 114-492 ng/mL | 114-492 ng/mL |
| 40-54 yrs | 90-360 ng/mL | 90-360 ng/mL |
| 55 yrs and over | 71-290 ng/mL | 71-290 ng/mL |

Values by Tanner Stage:

| TANNER STAGE | MALE | FEMALE |
|---|---|---|
| I | 109-485 ng/mL | 128-470 ng/mL |
| II | 174-512 ng/mL | 186-695 ng/mL |
| III | 230-818 ng/mL | 292-883 ng/mL |
| IV | 396-776 ng/mL | 394-920 ng/mL |
| V | 402-839 ng/mL | 308-1138 ng/mL |

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Lenexa, KS 66219-9752
(800) 646-7788

PATIENT: BONDS, BARRY
CLIENT PATIENT ID: ?
REQ NUMBER: 70146002-16
ID OR ROOM NO: UNKNOWN
PAGE DOB/AGE: Jul 24 1964/37 YEARS
3 SEX: M FASTING: YES HRS: 12
DATE/TIME COLL: Nov 08 2001 00:00
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BRIAN GOLDMAN, MD
1520 GILBRETH ROAD
BURLINGAME, CA 94010

| RESULT NAME | IN RANGE | OUT OF RANGE | REFERENCE | UNITS |
|---|---|---|---|---|

END OF REPORT FOR BONDS, BARRY

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# EXHIBIT D

GRAND JURY 04-1

NORTHERN DISTRICT OF CALIFORNIA

ORIGINAL

GJ INVESTIGATION NO. 2004R00608

REPORTER'S TRANSCRIPT OF PROCEEDINGS

TESTIMONY OF LARRY BOWERS

AT 450 GOLDEN GATE AVENUE

SAN FRANCISCO, CALIFORNIA 94102

THURSDAY, JUNE 29, 2006

FOR THE GOVERNMENT:

KEVIN V. RYAN,

UNITED STATES ATTORNEY

BY: JEFF NEDROW, AUSA

UNITED STATES DEPARTMENT OF JUSTICE

450 GOLDEN GATE AVENUE

SAN FRANCISCO, CALIFORNIA 94102

INDEX

LARRY BOWERS PAGE

Examination by MR. NEDROW 4

-o0o-

ALSO PRESENT (A.M. SESSION ONLY):

MATT A. PARRELLA, AUSA

JEFF FINIGAN, AUSA

steroids?

A. I am.

Q. And of these three classes, are any of those three classes prohibited as a controlled substance under federal law?

A. Right. Anabolic steroids are -- are part of the Controlled Substance Act, yes.

Q. But corticosteroids and the estrogen steroids are not actually under that act; correct?

A. They're -- they're certainly not under Category III, yeah. That's right. You -- you need a prescription for getting glucocortic -- some glucocorticoids, others you can get over the counter. So, yeah, that -- that's correct.

Q. Okay. You've referred to some of the effects of anabolic steroids, but let me -- let me go into that a little bit more. You referred to the -- the increased hair and the muscle mass. Are there other physical characteristics that can occur when one takes anabolic steroids?

A. Yes. There are -- there are a number of other things. I mean the -- the weight gain certainly would be something that -- that -- that would be apparent. Steroids also have an effect on -- on your sweat glands and -- and tend to have people develop acne; especially in the upper back is a characteristic of taking steroids. There are a number of other side effects that are negative.

I don't know whether you want me to do those, but those are two physical characteristics that you'd certainly see with -- with anabolic steroids.

Q. In men specifically, would there be any impact perceptible on the male genitalia in connection with taking steroids?

A. Correct. You'd definitely have a decrease in testicular size as a result of taking anabolic steroids, and that has to do with haltering your hormones in your body that control the production of sperm. So, yes, that's another effect that's almost universal.

Q. What about the impact on -- I guess from a physiological perspective, on a person's emotions or ability to control one's emotions? Is there a common term associated with that type of problem?

A. There's -- when you're on steroids, some people exhibit something that's called "roid rage," and, again, people tend to feel somewhat invincible, they tend to be much more aggressive when they're on steroids, and so that's definitely a -- a mental thing.

When you go off of steroids, frequently because your body isn't making any and you've stopped taking them, you -- you actually experience a depression and that can have a lot of -- of effects on -- on your lifestyle and other things also.

Q. Has the research -- we've talked about, I guess, side effects. Has the research suggested other possible or even documented negative consequences for parts of the body from the use or abuse of steroids?

A. Yeah, absolutely. One of the things, their effects on muscle, the heart muscle in particular and so people develop heart -- a weakness in their heart. There's the potential for hypertension, so you get elevated blood pressure from some steroids more so than others. There's an effect on the liver. I use the term "insult," meaning it's -- it -- it hurts the liver temporarily, but -- but some people are susceptible to longer-term effects like hepatic cancer.

That's rare, but it's definitely been linked to steroids, and we don't know -- one of the areas of -- of great concern that no one knows the answer to is long-term exposure of the prostate to -- to synthetic steroids; whether or not that might relate to prostate cancer, longer term, but there are not good studies on that.

Q. And what's the reason why there are some areas of a -- a lack of knowledge or ignorance as to what the effects might be in people over the long term? Is there a fairly apparent scientific reason why that is?

A. Yeah. I mean it -- one of the things that really hamstrungs -- strings those of us that follow the -- the rules of -- of both research and other things is that you would not be permitted to give the kinds of doses that we're talking about to -- to a human subject. Even with informed consent, you wouldn't get the permission to give those kinds of doses to people over a long period of time; so there's a real gap in what we can learn about long-term steroid abuse.

Q. And why aren't you permitted to give people large doses over long periods of time of steroids?

A. Well, it's because of the side effects that are known. There's -- it's felt that it's an un -- unreasonable risk to expose someone to that kind of steroid dose; especially if -- if it would be a woman, for example. There would be no way that you would -- that you would expose them to anabolic steroids for a long period of time.

Q. Because there's a concern of significant or possibly even fatal problems; correct?

A. Correct. Correct. Health problems, yes.

Q. Okay. Now, there are some reasons for which one can legitimately get a prescription for anabolic steroids; correct?

A. Correct.

Q. And you're not, of course, a -- though you obviously have a lot of academic experience from the research side. You're not a -- a doctor or a medical doctor.

A. I'm not a physician.

Q. A physician. Thank you. So, however, your research does give you some basis to understand the medical reasons a doctor might prescribe anabolic steroids.

A. Absolutely.

Q. Okay. So what might those be?

A. Any -- any disease that would -- that

A. It's a protein hormone; and just to back up a step and explain a bit, proteins are chains of amino acids that are put together. They then fold up into kind of a ball or a three-dimensional structure which then has an effect on different tissues. Growth hormone is secreted naturally in all of us. It has a lot of different metabolic effects. It interacts with the way you handle glucose, for example. It causes bone growth and cartilage growth. It causes muscle growth. It changes lipid metabolism in fat tissue.

So it -- it really is a very potent and far-reaching hormone in your body.

Q. And some of the same questions we asked earlier here. What are the effects of human growth hormone on the human body?

A. Obviously the -- the biggest one is growth. In -- before you're mature, before your long bones grow -- close at the ends, the growth hormone is responsible for height or stature. After that it has a whole series of effects. I mean it's -- again, it known to interact with -- with glucose, it affects your sleep, it affects a number of different kinds of behaviors as -- as part of its normal activity, but the main thing would be controlled bone growth, muscle growth.

Again, it would -- it would tend to make you leaner because it -- it tends to burn fat instead of accumulating it.

Q. Are there possible adverse side effects, for an adult anyway, with using human growth hormone without appropriate medical supervision?

A. Yeah, absolutely. A little bit different from steroids, which have some pretty acute or quick effects, the effects of growth hormone or the side effects of growth hormone tend to -- to occur over months or years instead of weeks let's say like they would for steroids. Obviously the -- the thing that usually -- there is a disease that you can sort of compare abuse of growth hormone to, and that's a disease called acromegaly which is -- which is simply an overproduction of growth hormone.

Those people are usually initially diagnosed by a physician because of growth of the fingers, hands, feet and also a change in ring size or maybe a change in hat size would be something that you would notice that would -- would lead a physician towards thinking you might have acromegaly.

Q. Again, with the caveat that you're not a -- a physician, is it normal for an adult's head or feet or hands after they've reached adulthood to -- to grow?

A. Not normally. No.

Q. And is -- that is something that with excessive human growth hormone in the body can occur?

A. Correct. Those bones -- I should make a distinction, perhaps, between two types of bones. The long bones like the ones in your legs and arms have growth plates at the ends of them and so once you finish puberty and you're mature, those plates close and your -- the bones in your arms and legs can't grow any longer at that point. The bones, for example, in your skull have two thin, hard layers on the outside and then sort of a spongy layer of bone on the inside.

The same is true for your fingers and -- and your toes and the small bones of your feet and hands. That spongy material is actually very stimulated by growth hormone and so your -- if you can think of it, your -- your skull bones actually swell if you want to think of it that way as opposed to, you know, growing together at the --

what are called the sutures where the bones come together. The -- the bones actually get thicker.

Q. So the head doesn't grow in the sense of adding inches up, but it would actually kind of swell or expand outward basically.

A. Correct.

Q. And on the hands and the feet can you use the same description? How does that work? Is there swelling outwards or just an extension or how does that work?

A. It's -- it's -- it's both. You grow a little bit longer in the -- in the bones, but you also get much bigger-boned in -- in your hands. Another place that's pretty typical of, again, making the analogy between acromegaly, which is a natural exposure, versus abuse, your jaw is another bone that tends to grow, again, because it doesn't have an end to it that -- that seals shut.

So your jaw would grow and your teeth, the spacing between your teeth would tend to change significantly if you're abusing growth hormone.

Q. What are the recognized -- and with human growth hormone, it's not classified under this anabolic or the federal Controlled Substances Act.

A. Correct.

of oxygen and your body turning into a different kind of metabolism that produces lactic acid, and -- and that's what burns. So that -- that would be EPO. Steroids and growth hormone both affect muscle mass and in the case of growth hormone, it also would make you -- it affects your fat tissue, so you would -- you would end up losing fat and putting on muscle as well.

There have been some other reports, for example, of -- of people actually having their eyesight improve from taking growth hormone, and that's thought to have something to do with the muscles that control your eye focus. So there are all kinds of ways and, again, not everyone gets every one of the benefits or the same amount of every benefit; but those are all things that would improve your performance athletically.

Q. Okay. And I think you addressed this, but I guess in a most obvious level, especially with a sport like football and potentially baseball and other sports, just having greater strength or a greater muscle response in terms of speed, those are the types of things that could assist; correct?

A. Yeah, absolutely. Again, some people

# EXHIBIT E

The New England Journal of Medicine

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VOLUME 335 JULY 4, 1996 NUMBER 1

# THE EFFECTS OF SUPRAPHYSIOLOGIC DOSES OF TESTOSTERONE ON MUSCLE SIZE AND STRENGTH IN NORMAL MEN

SHALENDER BHASIN, M.D., THOMAS W. STORER, PH.D., NANCY BERMAN, PH.D., CARLOS CALLEGARI, M.D., BRENDA CLEVENGER, B.A., JEFFREY PHILLIPS, M.D., THOMAS J. BUNNELL, B.A., RAY TRICKER, PH.D., AIDA SHIRAZI, R.PH., AND RICHARD CASABURI, PH.D., M.D.

## ABSTRACT

*Background* Athletes often take androgenic steroids in an attempt to increase their strength. The efficacy of these substances for this purpose is unsubstantiated, however.

*Methods* We randomly assigned 43 normal men to one of four groups: placebo with no exercise, testosterone with no exercise, placebo plus exercise, and testosterone plus exercise. The men received injections of 600 mg of testosterone enanthate or placebo weekly for 10 weeks. The men in the exercise groups performed standardized weight-lifting exercises three times weekly. Before and after the treatment period, fat-free mass was determined by underwater weighing, muscle size was measured by magnetic resonance imaging, and the strength of the arms and legs was assessed by bench-press and squatting exercises, respectively.

*Results* Among the men in the no-exercise groups, those given testosterone had greater increases than those given placebo in muscle size in their arms (mean [±SE] change in triceps area, 424±104 vs. −81±109 mm²; P<0.05) and legs (change in quadriceps area, 607±123 vs. −131±111 mm²; P<0.05) and greater increases in strength in the bench-press (9±4 vs. −1±1 kg, P<0.05) and squatting exercises (16±4 vs. 3±1 kg, P<0.05). The men assigned to testosterone and exercise had greater increases in fat-free mass (6.1±0.6 kg) and muscle size (triceps area, 501±104 mm²; quadriceps area, 1174±91 mm²) than those assigned to either no-exercise group, and greater increases in muscle strength (bench-press strength, 22±2 kg; squatting-exercise capacity, 38±4 kg) than either no-exercise group. Neither mood nor behavior was altered in any group.

*Conclusions* Supraphysiologic doses of testosterone, especially when combined with strength training, increase fat-free mass and muscle size and strength in normal men. (N Engl J Med 1996;335:1-7.)

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ANABOLIC–ANDROGENIC steroids are widely abused by athletes and recreational bodybuilders because of the perception that these substances increase muscle mass and strength,[1-9] but this premise is unsubstantiated. Testosterone replacement increases nitrogen retention and fat-free mass in castrated animals and hypogonadal men,[10-15] but whether supraphysiologic doses of testosterone or other anabolic–androgenic steroids augment muscle mass and strength in normal men is unknown.[1-9] Studies of the effects of such steroids on muscle strength have been inconclusive,[16-33] and several reviews have emphasized the shortcomings of the studies.[1-5,8-10] Some of the studies were not randomized; most did not control for intake of energy and protein; the exercise stimulus was often not standardized; and some studies included competitive athletes whose motivation to win may have kept them from complying with a standardized regimen of diet and exercise.

We sought to determine whether supraphysiologic doses of testosterone, administered alone or in conjunction with a standardized program of strength-training exercise, increase fat-free mass and muscle size and strength in normal men. To overcome the pitfalls of previous studies, the intake of energy and protein and the exercise stimulus were standardized. Because some previous studies had demonstrated significant increases in muscle strength and hyper-

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trophy in experienced athletes but not in sedentary subjects, we studied men who had weight-lifting experience.

## METHODS

### Study Design

This study was approved by the institutional review boards of the Harbor–UCLA Research and Education Institute and the Charles R. Drew University of Medicine and Science. All the study subjects gave informed written consent. The subjects were normal men weighing 90 to 115 percent of their ideal body weights; they were 19 to 40 years of age and had experience with weight lifting. They were recruited through advertisements in local newspapers and community colleges. None had participated in competitive sports in the preceding 12 months. Men who had ever taken anabolic agents or recreational drugs or had had a psychiatric or behavioral disorder were excluded from the study.

Of 50 men who were recruited, 7 dropped out during the control period because of problems with scheduling or compliance. The remaining 43 men were randomly assigned to one of four groups: placebo with no exercise, testosterone with no exercise, placebo plus exercise, and testosterone plus exercise. The study was divided into a 4-week control period, a 10-week treatment period, and a 16-week recovery period. During the four-week control period, the men were asked not to lift any weights or engage in strenuous aerobic exercise.

Of the 43 men, 3 dropped out during the treatment phase: 1 because of problems with compliance, 1 because illicit-drug use was detected by routine drug screening, and 1 because of an automobile accident. Forty men completed the study: 10 in the placebo, no-exercise group; 10 in the testosterone, no-exercise group; 9 in the placebo-plus-exercise group; and 11 in the testosterone-plus-exercise group.

### Standardization of Protein and Energy Intake

Two weeks before day 1, the men were instructed to begin following a standardized daily diet containing 36 kcal per kilogram of body weight, 1.5 g of protein per kilogram, and 100 percent of the recommended daily allowance of vitamins, minerals, and trace elements. Compliance with the diet was verified every four weeks by three-day records of food consumption. The dietary intake was adjusted every two weeks on the basis of changes in body weight.

### Treatment

The men received either 600 mg of testosterone enanthate in sesame oil or placebo intramuscularly each week for 10 weeks in the Clinical Research Center. This dose is six times higher than the dose usually given as replacement therapy in men with hypogonadism and is therefore supraphysiologic. Doses as high as 300 mg per week have been given to normal men for 16 to 24 weeks without major toxic effects.[34]

### Training Stimulus

The men in the exercise groups received controlled, supervised strength training three days per week during the treatment period. All the men trained at equivalent intensities in relation to their strength scores before the training. The training consisted of a cycle of weight lifting at heavy intensity (90 percent of the maximal weight the man lifted for one repetition before the start of training), light intensity (70 percent of the pretraining one-repetition maximal weight), and medium intensity (80 percent of this maximal weight) on three nonconsecutive days each week.[35] Regardless of the actual weights lifted, the training was held constant at four sets with six repetitions per set (a set is the number of complete repetitions of an exercise followed by rest). Because previous research had demonstrated increases in strength of approximately 7 percent for the bench-press exercise and 12 percent for the squatting exercise after four to five weeks of training,[35] the weights were increased correspondingly during the final five weeks of training in relation to the initial intensity. The number of sets was also increased from four to five, but the number of repetitions per set remained constant. The men were advised not to undertake any resistance exercise or moderate-to-heavy endurance exercise in addition to the prescribed regimen.

### Evaluation and Outcome Measures

The primary end points were fat-free mass, muscle size as measured by magnetic resonance imaging (MRI), and muscle strength as based on the one-repetition maximal weight lifted during the bench-press and squatting exercises before and after the 10-week treatment period. Serum concentrations of total and free testosterone, luteinizing hormone, follicle-stimulating hormone, and sex hormone–binding globulin were measured on days 14 and 28 of the control period and days 2, 3, 7, 14, 28, 42, 56, and 70 of the treatment period. Blood counts, blood chemistry (including serum aminotransferases), serum concentrations of prostate-specific antigen, and plasma concentrations of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured at the start of the control period and on day 4; on days 28, 56, and 70 of the treatment period; and four months after the discontinuation of treatment. Periodic evaluations to identify adverse effects were performed by examiners unaware of the study-group assignments on days 1 and 28 of the control period; days 28, 56, and 70 of the treatment period; and four months after the discontinuation of treatment. Mood and behavior were evaluated during the first week of the control period and after 6 and 10 weeks of treatment. Sexual function and semen characteristics were not assessed.

### Assessment of Muscle Size

Muscle size was measured by MRI of the arms and legs at the humeral or femoral mid-diaphyseal level, the junction of the upper third and middle third of the bone, and the junction of the middle third and lower third. The cross-sectional areas of the arms and legs, the subcutaneous tissue, the muscle compartment, and the quadriceps and triceps muscles were computed, and the areas at the three levels were averaged.

### Analysis of Body Composition

Fat-free mass was estimated on the basis of measurements of body density obtained by underwater weighing. During weighing, the men were asked to exhale to the residual volume, as measured by helium dilution.

### Measures of Muscle Strength

The effort-dependent performance of muscle was assessed on the basis of the maximal weight lifted for one repetition during the bench-press and squatting exercises.[36] Each man completed increasingly more difficult lifts with the same weights and bars that he used during training; in each exercise, the maximal weight lifted (the one-repetition maximum) was recorded as a measure of muscle strength.

### Hormone Measurements

Serum concentrations of luteinizing hormone and follicle-stimulating hormone were measured by immunofluorometric assays,[36] each with a sensitivity of 0.05 IU per liter. Serum testosterone was measured by immunoassay,[37] and free testosterone was measured by equilibrium dialysis.[37] Serum concentrations of sex hormone–binding globulin and prostate-specific antigen were measured by immunoassays using reagents purchased from Delphia–Wallac (Turku, Finland) and Hybritech (San Diego, Calif.), respectively.

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**Table 1.** Base-Line Characteristics of the Study Subjects.*

| Group | Age | Weight | Height | Body-Mass Index† |
|---|---|---|---|---|
| | yr | kg | cm | |
| No exercise | | | | |
| Placebo | 27±5 | 79.5±13.6 | 177.5±7.7 | 25.1±2.9 |
| Testosterone | 26±6 | 82.2±6.0 | 177.1±7.2 | 26.4±3.1 |
| Exercise | | | | |
| Placebo | 26±6 | 85.5±9.7 | 181.0±5.8 | 26.2±3.2 |
| Testosterone | 30±7 | 76.0±10.0 | 175.6±6.4 | 24.6±2.9 |

*Plus–minus values are means ±SD.

†Calculated as the weight in kilograms divided by the square of the height in meters.

### Assessment of Mood and Behavior

A standardized Multidimensional Anger Inventory[38] that includes 38 questions to measure the frequency, duration, magnitude, and mode of expression of anger, arousal of anger, hostile outlook, and anger-eliciting situations and a Mood Inventory that includes questions pertaining to general mood, emotional stability, and angry behavior were administered before, during (week 6), and after the treatment (unpublished data). For each man a live-in partner, spouse, or parent answered the same questions about the man's mood and behavior.

### Statistical Analysis

The Shapiro and Wilk test was used to test whether the outcome variables had a normal distribution. Changes were computed for each subject as the difference between the values for each variable at the beginning and end of the treatment period (from day 0 to day 70). These values were averaged among the subjects in each group to obtain the group means. Analysis of variance was used to determine whether there were base-line differences among the four groups. Two-tailed, paired t-tests were used to test for changes in each outcome variable in each group. If there was a change, an analysis of variance was used to test for differences between groups in the amount of change, and then Scheffé's test was used to assess pairwise differences. This test adjusts for multiple comparisons, but it does not yield exact P values for pairwise comparisons between groups.

## RESULTS

The four groups were similar with respect to age and weight, height, and body-mass index before treatment (Table 1). Acne developed in three men receiving testosterone and one receiving placebo, and two men receiving testosterone reported breast tenderness, but no other side effects were noted. The serum liver-enzyme concentrations, hemoglobin concentrations, hematocrits, and red-cell counts did not change in any study group (Table 2). Serum creatinine concentrations did not change, except in the testosterone-plus-exercise group, in which the mean (±SE) serum creatinine concentration increased from 1.0 mg per deciliter (88 μmol per liter) to 1.1 mg per deciliter (97 μmol per liter) ($P=0.02$). Plasma concentrations of total and LDL cholesterol and triglycerides did not change in any study group; plasma HDL cholesterol decreased significantly in the placebo-plus-exercise group. There was no change in the serum concentration of prostate-specific antigen in any group.

### Endocrine Responses

The base-line serum concentrations of total and free testosterone in the four groups were similar. The serum concentrations of total and free testosterone increased significantly in the two testosterone

**Table 2.** Hemoglobin and Plasma Lipid Concentrations before and after the 10 Weeks of Treatment.*

| Variable | No Exercise | | Exercise | |
|---|---|---|---|---|
| | Placebo | Testosterone | Placebo | Testosterone |
| Hemoglobin (g/dl) | | | | |
| Base line | 14.9±0.2 | 15.1±0.2 | 14.5±0.3 | 15.3±0.4 |
| 10 wk | 15.0±0.3 | 15.5±0.2 | 14.3±0.4 | 15.7±0.2 |
| HDL cholesterol (mg/dl) | | | | |
| Base line | 39±2 | 37±3 | 42±3 | 40±2 |
| 10 wk | 36±3 | 34±3 | 37±3† | 36±3 |
| LDL cholesterol (mg/dl) | | | | |
| Base line | 113±10 | 133±7 | 117±6 | 128±12 |
| 10 wk | 116±11 | 133±9 | 115±7 | 121±10 |
| Triglycerides (mg/dl) | | | | |
| Base line | 155±36 | 147±25 | 105±14 | 146±15 |
| 10 wk | 139±27 | 111±13 | 104±21 | 125±15 |

*Plasma lipid concentrations were measured in 9 men assigned to placebo with no exercise, 8 men assigned to testosterone with no exercise, 8 men assigned to placebo plus exercise, and 10 men assigned to testosterone plus exercise. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein. To convert values for hemoglobin to millimoles per liter, multiply by 0.62; to convert values for cholesterol to millimoles per liter, multiply by 0.02586; and to convert values for triglycerides to millimoles per liter, multiply by 0.0113. Plus–minus values are means ±SE.

†P = 0.04 for the comparison with the base-line value.

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**TABLE 3.** SERUM CONCENTRATIONS OF ENDOCRINE HORMONES IN THE STUDY SUBJECTS BEFORE AND AFTER THE 10 WEEKS OF TREATMENT.*

| HORMONE | NO EXERCISE | | EXERCISE | |
|---|---|---|---|---|
| | PLACEBO | TESTOSTERONE | PLACEBO | TESTOSTERONE |
| Total testosterone (ng/dl) | | | | |
| Base line | 516±58 | 502±63 | 557±45 | 431±38 |
| 10 wk | 453±35 | 2828±417†‡ | 667±117 | 3244±305†‡ |
| Free testosterone (pg/ml) | | | | |
| Base line | 74±7 | 79±7 | 83±7 | 90±6 |
| 10 wk | 74±13 | 497±62†‡ | 81±9 | 572±53†‡ |
| Luteinizing hormone (mIU/ml) | | | | |
| Base line | 3.3±0.4 | 3.8±0.6 | 4.0±0.7 | 3.3±0.5 |
| 10 wk | 4.3±0.9 | 0.4±0.2†‡ | 4.4±1.1 | 0.4±0.2†‡ |
| Follicle-stimulating hormone (mIU/ml) | | | | |
| Base line | 3.1±0.3 | 3.1±0.4 | 3.2±0.6 | 3.0±0.6 |
| 10 wk | 2.7±0.3 | 0.3±0.2†‡ | 4.4±1.1 | 0.10±0.03†‡ |
| Sex hormone–binding globulin (ng/dl) | | | | |
| Base line | 224±33 | 256±34 | 353±41 | 271±43 |
| 10 wk | 244±53 | 176±24‡§ | 320±31 | 201±34‡¶ |

*Values at 10 weeks were obtained 1 week after the final injection. To convert values for total testosterone to nanomoles per liter, multiply by 0.0347; to convert values for free testosterone to picomoles per liter, multiply by 3.47; to convert values for sex hormone–binding globulin to nanomoles per liter, multiply by 0.12. Plus–minus values are means ±SE.

†P<0.001 for the comparison with the corresponding base-line value.

‡P<0.05 for the comparison of the difference between this value and the base-line value with the corresponding difference in either placebo group.

§P=0.008 for the comparison with the corresponding base-line value.

¶P=0.05 for the comparison with the corresponding base-line value.

groups, but not in the placebo groups (Table 3). The base-line serum concentrations of luteinizing hormone, follicle-stimulating hormone, and sex hormone–binding globulin were similar in the four groups, and the concentrations decreased significantly in the two testosterone groups.

#### Body Weight and Composition

Body weight did not change significantly in the men in either placebo group (Table 4). The men given testosterone without exercise had a significant mean increase in total body weight, and those in the testosterone-plus-exercise group had an average increase of 6.1 kg in body weight — a greater increase than in the other three groups.

Fat-free mass did not change significantly in the group assigned to placebo but no exercise (Table 4 and Fig. 1). The men treated with testosterone but no exercise had an increase of 3.2 kg in fat-free mass, and those in the placebo-plus-exercise group had an increase of 1.9 kg. The increase in the testosterone-plus-exercise group was substantially greater (averaging 6.1 kg). The percentage of body fat did not change significantly in any group (data not shown).

#### Muscle Size

The mean cross-sectional areas of the arm and leg muscles did not change significantly in the placebo groups, whether the men had exercise or not (Table 4 and Fig. 1). The men in the testosterone groups had significant increases in the cross-sectional areas of the triceps and the quadriceps (Table 4); the group assigned to testosterone without exercise had a significantly greater increase in the cross-sectional area of the quadriceps than the placebo-alone group, and the testosterone-plus-exercise group had greater increases in quadriceps and triceps area than either the testosterone-alone or the placebo-plus-exercise group (P<0.05).

#### Muscle Strength

Muscle strength in the bench-press and the squatting exercises did not change significantly over the 10-week period in the group assigned to placebo with no exercise. The men in the testosterone-alone and placebo-plus-exercise groups had significant increases in the one-repetition maximal weights lifted in the squatting exercises, averaging 19 percent and 21 percent, respectively (Table 4 and Fig. 1). Similarly, mean bench-press strength increased in these two groups by 10 percent and 11 percent, respectively. In the testosterone-plus-exercise group, the increase in muscle strength in the squatting exercise (38 percent) was greater than that in any other group, as was the increase in bench-press strength (22 percent).

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TABLE 4. BODY WEIGHT, FAT-FREE MASS, AND MUSCLE SIZE AND STRENGTH BEFORE AND AFTER THE 10 WEEKS OF TREATMENT.*

| VARIABLE | NO EXERCISE | | EXERCISE | |
|---|---|---|---|---|
| | PLACEBO | TESTOSTERONE | PLACEBO | TESTOSTERONE |
| Body weight (kg) | | | | |
| Base line | 79.5±4.3 | 82.2±1.9 | 85.5±3.3 | 76.0±3.0 |
| 10 wk | 80.8±4.4 | 85.7±1.5 | 86.4±2.9 | 82.0±2.8† |
| P value | — | 0.004 | — | <0.001 |
| Fat-free mass (kg) | | | | |
| Base line | 65.1±2.5 | 69.9±1.3 | 72.1±2.3 | 65.3±1.8 |
| 10 wk | 65.9±2.7 | 73.1±2.2 | 74.1±2.2 | 71.4±1.8‡ |
| P value | — | — | 0.017 | <0.001 |
| Triceps area (mm²) | | | | |
| Base line | 3621±213 | 3579±260 | 4,052±262 | 3483±217 |
| 10 wk | 3539±226 | 4003±229§ | 4,109±230 | 3984±239§ |
| P value | — | 0.003 | — | <0.001 |
| Quadriceps area (mm²) | | | | |
| Base line | 8796±561 | 9067±398 | 9,920±569 | 8550±353 |
| 10 wk | 8665±481 | 9674±472§ | 10,454±474§ | 9724±348¶ |
| P value | — | <0.001 | — | <0.001 |
| Bench-press exercise (kg lifted) | | | | |
| Base line | 88±5 | 96±8 | 109±12 | 97±6 |
| 10 wk | 88±5 | 105±8§ | 119±11§ | 119±6‡ |
| P value | — | — | 0.005 | <0.001 |
| Squatting exercise (kg lifted) | | | | |
| Base line | 102±6 | 103±8 | 126±13 | 102±5 |
| 10 wk | 105±6 | 116±5 | 151±13§ | 140±5¶ |
| P value | — | 0.004 | <0.001 | <0.001 |

*P values are shown for the comparison of the 10-week values with the base-line values when P≤0.05. Plus–minus values are means ±SE.

†P<0.05 for the comparison of the change from base line with that in either placebo group.

‡P<0.05 for the comparison of the change from base line with that in either no-exercise group.

§P<0.05 for the comparison of the change from base line with that in the group assigned to placebo with no exercise.

¶P<0.05 for the comparison of the change from base line with that in the other three groups.

### Mood and Behavior

No differences were found between the exercise groups and the no-exercise groups or between the placebo groups and the testosterone groups in any of the five subcategories of anger assessed by the Multidimensional Anger Inventory. No significant changes in mood or behavior were reported by the men on the Mood Inventory or by their live-in partners, spouses, or parents on the Observer Mood Inventory.

## DISCUSSION

Our results show that supraphysiologic doses of testosterone, especially when combined with strength training, increase fat-free mass, muscle size, and strength in normal men when potentially confounding variables, such as nutritional intake and exercise stimulus, are standardized. The combination of strength training and testosterone produced greater increases in muscle size and strength than were achieved with either intervention alone. The combined regimen of testosterone and exercise led to an increase of 6.1 kg in fat-free mass over the course of 10 weeks; this increase entirely accounted for the changes in body weight.

The exercise was standardized in all the men, and therefore the effects of testosterone on muscle size and strength cannot be attributed to more intense training in the groups receiving the treatment. Careful selection of experienced weight lifters, the exclusion of competitive athletes, and close follow-up ensured a high degree of compliance with the regimens of exercise, treatment, and diet, which was verified by three-day food records (data not shown) and the values obtained for serum testosterone, luteinizing hormone, and follicle-stimulating hormone. Except for one man who missed one injection, all the men received all their scheduled injections. It has been argued that studies in which large doses of androgens are used cannot be truly blinded because of the occurrence of acne or other side effects. In this study, neither the investigators nor the personnel performing the measurements knew the study-group assignments. Three men receiving testosterone and one man receiving placebo had acneiform eruptions; these men may have assumed themselves to be receiving testosterone. Thus, it cannot be stated with certainty

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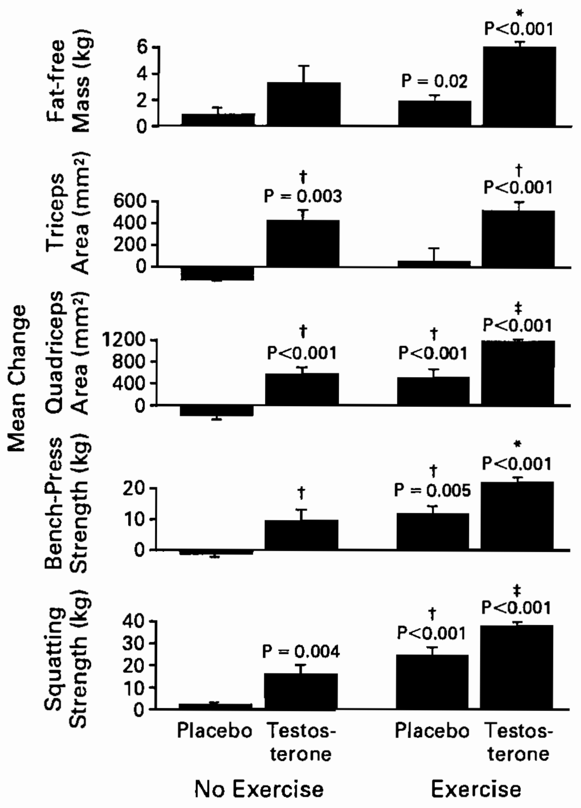

**Figure 1.** Changes from Base Line in Mean (±SE) Fat-free Mass, Triceps and Quadriceps Cross-Sectional Areas, and Muscle Strength in the Bench-Press and Squatting Exercises over the 10 Weeks of Treatment.

The P values shown are for the comparison between the change indicated and a change of zero. The asterisks indicate P<0.05 for the comparison between the change indicated and that in either no-exercise group; the daggers, P<0.05 for the comparison between the change indicated and that in the group assigned to placebo with no exercise; and the double daggers, P<0.05 for the comparison between the change indicated and the changes in all three other groups.

that the men were completely unaware of the nature of their treatments.

The doses of androgenic steroids used in previous studies were low,[1-5,11,12] mostly because of concern about potential toxic effects. In contrast, to our knowledge the dose of testosterone enanthate administered in this study (600 mg per week) is the highest administered in any study of athletic performance. Undoubtedly, some athletes and bodybuilders take even higher doses than those we gave. Furthermore, athletes often "stack" androgenic and anabolic steroids, taking multiple forms simultaneously. We do not know whether still higher doses of testosterone or the simultaneous administration of several steroids would have more pronounced effects. The absence of systemic toxicity during testosterone treatment was consistent with the results of studies of the contraceptive efficacy of that hormone.[34]

The method used in this study to evaluate muscle performance on the basis of the one-repetition maximal weight lifted is dependent on effort. Although the men receiving testosterone did have increases in muscle size, some of the gains in strength may have resulted from the behavioral effects of testosterone.

The dose dependency of the action of testosterone on fat-free mass and protein synthesis has not been well studied. Forbes[39] proposed a single dose–response curve extending from the hypogonadal to the supraphysiologic range. Others have suggested that there may be two dose–response curves: one in the hypogonadal range, with maximal responses corresponding to the serum testosterone concentrations at the lower end of the range in normal men, and the second in the supraphysiologic range, presumably representing a separate mechanism of action — that is, a pathway of independent androgen receptors.[1,40]

Supraphysiologic doses of testosterone, with or without exercise, did not increase the occurrence of angry behavior by these carefully selected men in the controlled setting of this experiment. Our results, however, do not preclude the possibility that still higher doses of multiple steroids may provoke angry behavior in men with preexisting psychiatric or behavioral problems.

Our results in no way justify the use of anabolic–androgenic steroids in sports, because, with extended use, such drugs have potentially serious adverse effects on the cardiovascular system, prostate, lipid metabolism, and insulin sensitivity. Moreover, the use of any performance-enhancing agent in sports raises serious ethical issues. Our findings do, however, raise the possibility that the short-term administration of androgens may have beneficial effects in immobilized patients, during space travel, and in patients with cancer-related cachexia, disease caused by the human immunodeficiency virus, or other chronic wasting disorders.

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# EXHIBIT F

**Annals of Internal Medicine** | REVIEW

# Systematic Review: The Effects of Growth Hormone on Athletic Performance

Hau Liu, MD, MBA, MPH; Dena M. Bravata, MD, MS; Ingram Olkin, PhD; Anne Friedlander, PhD; Vincent Liu, MD; Brian Roberts, MD; Eran Bendavid, MD, MPH; Olga Saynina, MA, MBA; Shelley R. Salpeter, MD; Alan M. Garber, MD, PhD; and Andrew R. Hoffman, MD

Background: Human growth hormone is reportedly used to enhance athletic performance, although its safety and efficacy for this purpose are poorly understood.

Purpose: To evaluate evidence about the effects of growth hormone on athletic performance in physically fit, young individuals.

Data Sources: MEDLINE, EMBASE, SPORTDiscus, and Cochrane Collaboration databases were searched for English-language studies published between January 1966 and October 2007.

Study Selection: Randomized, controlled trials that compared growth hormone treatment with no growth hormone treatment in community-dwelling healthy participants between 13 and 45 years of age.

Data Extraction: 2 authors independently reviewed articles and abstracted data.

Data Synthesis: 44 articles describing 27 study samples met inclusion criteria; 303 participants received growth hormone, representing 13.3 person-years of treatment. Participants were young (mean age, 27 years [SD, 3]), lean (mean body mass index, 24 kg/m$^2$ [SD, 2]), and physically fit (mean maximum oxygen uptake, 51 mL/kg of body weight per minute [SD, 8]). Growth hormone dosage (mean, 36 μg/kg per day [SD, 21]) and treatment duration (mean, 20 days [SD, 18] for studies giving growth hormone for >1 day) varied. Lean body mass increased in growth hormone recipients compared with participants who did not receive growth hormone (increase, 2.1 kg [95% CI, 1.3 to 2.9 kg]), but strength and exercise capacity did not seem to improve. Lactate levels during exercise were statistically significantly higher in 2 of 3 studies that evaluated this outcome. Growth hormone–treated participants more frequently experienced soft tissue edema and fatigue than did those not treated with growth hormone.

Limitations: Few studies evaluated athletic performance. Growth hormone protocols in the studies may not reflect real-world doses and regimens.

Conclusion: Claims that growth hormone enhances physical performance are not supported by the scientific literature. Although the limited available evidence suggests that growth hormone increases lean body mass, it may not improve strength; in addition, it may worsen exercise capacity and increase adverse events. More research is needed to conclusively determine the effects of growth hormone on athletic performance.

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For author affiliations, see end of text.

The use of human growth hormone to improve athletic performance has recently received worldwide attention. This practice, often called *sports doping*, is banned by most professional sports leagues and associations, including the International Olympic Committee, Major League Baseball, and the National Football League (1–3). However, a wide range of athletes, including those from baseball (4–6), cycling (7, 8), and track and field (5, 9), have been implicated in or have confessed to illicit growth hormone use. The Mitchell report (10) recently identified 89 Major League Baseball players who allegedly used performance-enhancing drugs, and some of these players have subsequently admitted to using growth hormone (11, 12).

Part of the attraction of using growth hormone as a performance enhancer has been that its use is difficult to detect. The World Anti-Doping Agency, whose formation stemmed from the widely publicized doping scandal of the 1998 Tour de France (13), first used a blood test to detect exogenous growth hormone during the 2004 Olympic Games in Athens. However, according to the World Anti-Doping Agency, there have been no test-confirmed positive cases for growth hormone doping in professional or Olympic athletes (14), probably because of the limited availability and implementation of this test.

Although growth hormone is reportedly used to enhance athletic performance and has been called the "most anabolic substance known" (15), its efficacy for this purpose is not well established. Some have suggested that growth hormone is a "wonder drug" (16) that results in "ripped muscle" (17) and provides "stamina-increasing properties" (18). Exogenous growth hormone therapy in growth hormone–deficient adults (that is, those with growth hormone deficiency due to hypothalamic or pituitary defects) results in increased lean mass and decreased fat mass (19), and comparable body composition changes are seen in healthy elderly adults who receive growth hormone (20). Some experts, however, have suggested that the strength-enhancing properties of growth hormone among healthy adults have been exaggerated (15). Serious side effects, including diabetes, hepatitis, and acute renal failure, may occur in athletes using high-dose growth hormone (21). Furthermore, the use of growth hormone

*See also:*

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Appendix Tables
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for athletic enhancement is not approved by the U.S. Food and Drug Administration, and the distribution of growth hormone for this purpose is illegal in the United States (22).

We performed a systematic review of randomized, controlled trials to determine the effects of growth hormone therapy on athletic performance in healthy, physically fit, young adults. Our primary aim was to evaluate the effects of growth hormone on body composition, strength, basal metabolism, and exercise capacity. In addition, we sought to synthesize the evidence on adverse events associated with growth hormone in the healthy young and assess the quality of the published literature.

## METHODS

### Literature Searches

In consultation with 2 research librarians, we developed individual search strategies to identify potentially relevant studies from the MEDLINE, EMBASE, SPORTDiscus, and Cochrane Collaboration databases. We sought English-language reports indexed through 11 October 2007 with keywords including *growth hormone* and *randomized controlled trial* (Appendix Table 1, available at www.annals.org). We searched bibliographies of retrieved articles for additional studies.

### Study Selection

We sought randomized, controlled trials, including crossover trials, that compared growth hormone therapy with no growth hormone therapy. We included studies that 1) evaluated at least 5 participants, 2) enrolled only community-dwelling participants, 3) assessed participants with a mean or median age between 13 and 45 years, and 4) provided data on at least 1 clinical outcome of interest. We excluded studies that 1) focused solely on evaluating growth hormone secretagogues, 2) explicitly included patients with any comorbid medical condition, or 3) evaluated growth hormone as treatment for a specific illness (for example, adult growth hormone deficiency or fibromyalgia).

### Data Abstraction

One author reviewed the titles and abstracts of articles identified through our search and retrieved potentially relevant studies. An endocrinologist and a physician with training in meta-analytic techniques separately reviewed the retrieved studies and abstracted data independently onto pretested abstraction forms. We resolved abstraction differences by repeated review and consensus. If a study did not present data necessary for analysis or mentioned results but did not present data, we requested additional data from study authors. If data were presented graphically, we used the graph-digitizing program DigitizeIt, version 1.5 (Share It, Braunschweig, Germany), to abstract data from the graph (23). If multiple studies presented findings from the same cohort, we used these data only once in our analysis.

We abstracted 4 types of data from each study: participant characteristics (for example, age, sex, body mass index, baseline maximum oxygen uptake [$VO_2$max]), study interventions (for example, dose, route, frequency, and duration of growth hormone therapy), study quality (for example, quality of randomization and blinding) (24, 25), and clinical outcomes. We included studies that provided data on at least 1 of the following clinical outcomes: body composition (for example, body weight, lean body mass, fat mass), strength (for example, biceps or quadriceps strength), basal metabolism (for example, resting energy expenditure, basal metabolic rate, heart rate, respiratory exchange ratio, or respiratory quotient), exercise capacity (for example, exercising lactate levels, exercising respiratory exchange ratio or respiratory quotient, maximum inspiratory pressure, bicycling speed, and $VO_2$max), or adverse events. Because the terms *lean body mass* and *fat-free mass* are typically used interchangeably in the literature, we report fat-free mass and lean body mass data as a single category of lean body mass. Similarly, we report resting energy expenditure and basal metabolic rate as a single category of basal metabolic rate.

### Quantitative Data Synthesis

To describe key study characteristics, we computed mean values weighted by the number of participants in the trial. To evaluate the effects of growth hormone on body composition and strength, we computed a change score for each clinical outcome for both the treatment and control groups as the value of the outcome at trial end minus the value of the outcome at trial start. We used these change scores to calculate the weighted mean difference and standard mean difference (26) effect sizes. The weighted mean difference is reported in the same units as the clinical outcome of interest, thereby facilitating clinical interpretation. Because our outcomes were similar for both methods, we present only the outcomes from the weighted mean difference method. For studies that did not report the variance of an outcome at trial end minus the value at trial start, we calculated it as the sum of the trial-start and trial-end variances minus twice the covariance (20, 27). Because trial-start data were not available for most of the studies reporting basal metabolic outcomes, we compared trial-end results between treatment and control groups for these outcomes. We combined studies by using random-effects models (26–28) because of potential interstudy heterogeneity.

The considerable variability in exercise protocols used in the included studies reporting exercise capacity outcomes made pooling these results inappropriate. Instead, we provide a narrative, qualitative assessment of exercise capacity outcomes and report their associated published $P$ values.

The variability in reporting adverse events among included studies also made a quantitative meta-analysis of these outcomes inappropriate. Instead, we calculated the proportions of adverse events among participants who received and did not receive growth hormone in studies that reported or evaluated for each adverse event.

We performed sensitivity analyses and assessed interstudy heterogeneity to evaluate the robustness of our results. We removed each study individually to evaluate that study's effect on the summary estimates. We assessed publication bias by constructing funnel plots and calculated the number of unpublished studies required to statistically significantly change our results (28). We assessed heterogeneity among study results for each of the summary effects by calculating the $Q$ statistic (and associated $P$ value) and $I^2$ statistic (26, 28–30). We evaluated heterogeneity through predetermined subgroup analysis that stratified studies by duration of treatment. We performed analyses by using Stata software, version 9.1 (Stata, College Station, Texas); SPSS, version 15.0 (SPSS, Chicago); and Comprehensive Meta-Analysis, version 2 (Biostat, Englewood, New Jersey). We considered $P$ values less than 0.05 (2-tailed) to indicate statistically significant differences.

### Role of the Funding Source

The authors were supported in part or fully by the Agency for Healthcare Research and Quality, Santa Clara Valley Medical Center, the U.S. Department of Veteran Affairs, Stanford University Medical Center, Stanford University, Genentech, the National Science Foundation, and the Evidence-Based Medicine Center of Excellence of Pfizer. These funding sources had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

## RESULTS

The **Figure** summarizes the results of our literature searches. We reviewed 7599 titles from the MEDLINE, EMBASE, SPORTDiscus, and the Cochrane Collaboration databases. From our search, we reviewed 252 abstracts in detail and retrieved 56 articles for full-text evaluation. We identified 3 additional studies through searches of bibliographies. Multiple articles were often published on the same study sample: 44 articles representing 27 study samples met our inclusion criteria (Table 1) (31–74).

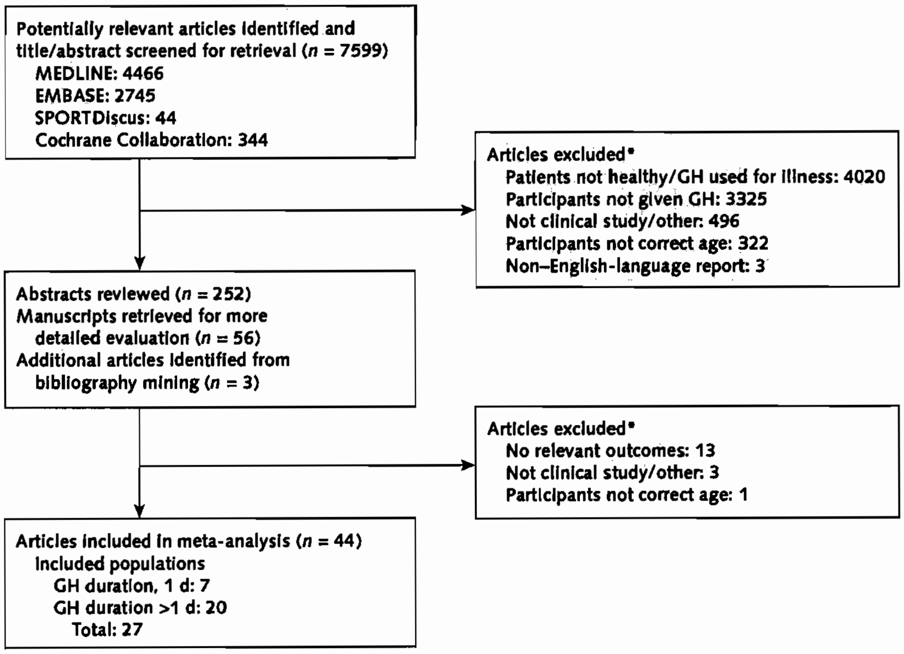
### Participant Characteristics

Study participants were predominantly male (85%), young (mean age, 27 years [SD, 3]), lean (mean body mass index, 24 kg/m$^2$ [SD, 2]), and physically fit (mean $VO_2$max, 51 mL/kg per minute [SD, 8]; range, 38 to 65 mL/kg per minute) (Table 1).

### Study Characteristics

The included studies enrolled 440 participants. Of these, 303 received growth hormone treatment, representing 13.3 person-years of treatment (Table 1). Study sizes were generally small (mean number of participants at enrollment, 15), and dropout rates were low (98% of participants completed the study protocols).

*Figure.* **Study flow diagram.**


Potentially relevant articles identified and title/abstract screened for retrieval (n = 7599)
MEDLINE: 4466
EMBASE: 2745
SPORTDiscus: 44
Cochrane Collaboration: 344
Articles excluded*
Patients not healthy/GH used for illness: 4020
Participants not given GH: 3325
Not clinical study/other: 496
Participants not correct age: 322
Non–English-language report: 3
Abstracts reviewed (n = 252)
Manuscripts retrieved for more detailed evaluation (n = 56)
Additional articles identified from bibliography mining (n = 3)
Articles excluded*
No relevant outcomes: 13
Not clinical study/other: 3
Participants not correct age: 1
Articles included in meta-analysis (n = 44)
Included populations
GH duration, 1 d: 7
GH duration >1 d: 20
Total: 27

GH = growth hormone. *Sum may be greater than total number excluded because some studies had multiple reasons for exclusion.

*Table 1.* Baseline Characteristics of Participants and Study Intervention*

| Study, Year (Reference) | Mean Age (SD), y | | Men, % | | Sample Size at Start and End of Study, n/n† | |
|---|---|---|---|---|---|---|
| | Growth Hormone Group | Control Group | Growth Hormone Group | Control Group | Growth Hormone Group | Control Group |
| **Single-dose growth hormone** | | | | | | |
| Gravhølt et al., 1999 (34)‡ | 25.5 (3.7) | 25.5 (3.7) | 100 | 100 | 8/8 | 8/8 |
| Hansen et al., 2005 (1 d) (35)‡ | 25.1 (5.7) | 25.1 (5.7) | 100 | 100 | 8/7 | 8/7 |
| Hashimoto et al., 2000 (36) | 20–31‖ | 20–31‖ | 100 | 100 | 24/24 | 8/8 |
| Irving et al., 2004 (37)‡ | 23.7 (5.7) | 23.7 (5.7) | 100 | 100 | 9/9 | 9/9 |
| Lange et al., 2002 (38)‡ | 26.0 (2.6) | 26.0 (2.6) | 100 | 100 | 7/5** | 7/7 |
| Møller et al., 1990 (39)‡ | 29.0 (2.4) | 29.0 (2.4) | 100 | 100 | 6/6 | 6/6 |
| Napoli et al., 2003 (40)‡ | 22.0 (2.8) | 22.0 (2.8) | 75 | 75 | 8/8 | 8/8 |
| **Multiple-dose growth hormone** | | | | | | |
| Brixen et al., 1990, 1992, 1995 (41–43) | 26.0 (NA) [22–31‖] | 27.0 (NA) [22–30‖] | 100 | 100 | 10/9 | 10/10 |
| Crist et al., 1988, 1990, 1991 (44–46)‡ | 27.9 (3.7) | 27.9 (3.7) | 63 | 63 | 8/8 | 8/8 |
| Deyssig et al., 1993 (47) | 23.4 (2.8)‡‡ | 23.4 (2.8)‡‡ | 100 | 100 | 11/8 | 11/10 |
| Ehrnborg et al., 2005 (33, 48) | 25.6 (4.2) | 27.0 (4.4) | 50 | 50 | 20/20 | 10/10 |
| Giannoulis et al., 2005, 2002, 2000, 2000 (49–52) | 25.0 (9.8)/26.3 (9.8)§§ | 24.9 (5.6)/24.0 (5.6)§§ | 51 | 53 | 39/39‖‖ | 30/30‖‖ |
| Graham et al., 2007 (72–74) | 32 (9) | 32 (11) | 100 | 100 | 24/24 | 24/24 |
| Hansen et al., 2001 (53)‡ | 26.1 (NA) [23–31‖] | 26.1 (NA) [23–31‖] | 100 | 100 | 8/8 | 8/8 |
| Hansen et al., 2005 (32) | 24.0 (4.0) | 25.0 (4.0) | 100 | 100 | 8/8 | 8/8 |
| Healy et al., 2006, 2003 (54, 55) | 31 (NA) [23–40‖] | 33 (NA) [27–42‖] | 100 | 100 | 6/6 | 6/6 |
| Horber et al., 1993, 1991 (31, 56) | 18–36‖‡‡ | 18–36‖‡‡ | 100††† | 100††† | 8/8 | 8/8 |
| Kniess et al., 2003 (57) | 24 (NA) [21–33‖]¶¶ | 24 (NA) [21–33‖]¶¶ | 100 | 100 | 10/10 | 5/5 |
| Møller et al., 1991 (58)‡ | 27.1 (NA) [21–33‖] | 27.1 (NA) [21–33‖] | 100 | 100 | 8/8 | 8/8 |
| Møller et al., 1992 (59)‡ | 26 (NA) [21–33‖] | 26 (NA) [21–33‖] | 57 | 57 | 14/14 | 14/14 |
| Møller et al., 1993 (60)‡ | 28.0 (2.4) | 28.0 (2.4) | 0 | 0 | 6/6 | 6/6 |
| Møller et al., 1995, 1996 (61, 62)‡ | 26.5 (2.7) | 26.5 (2.7) | 100 | 100 | 8/8 | 8/8 |
| Wallace et al., 2001, 2001, 1999 (63–65) | 28.3 (11.2) | 25.5 (6.0) | 100 | 100 | 8/8 | 8/8 |
| Wolthers et al., 1999, 1996, 1996 (66–68)‡ | 19–29‖ | 19–29‖ | 100 | 100 | 8/8 | 8/8 |
| Wolthers et al., 1998 (69)‡ | 22–28‖ | 22–28‖ | 100 | 100 | 8/8 | 8/8 |
| Yarasheski et al., 1992 (70) | 27.0 (4.2)‡‡ | 27.0 (4.2)‡‡ | 100 | 100 | 9/7 | 9/9 |
| Yuen et al., 2004 (71)‡ | 19–29‖ | 19–29‖ | 58 | 58 | 12/12 | 12/12 |

* The section on single-dose growth hormone includes studies that provided 1 dose of growth hormone therapy; the section on multiple-dose growth hormone includes studies that provided growth hormone for >1 day. In each section, references are arranged in alphabetical order. BMI = body mass index; NA = not available/unclear; $VO_2max$ = maximum oxygen uptake.
† Total does not add up to 440 participants because some studies had crossover designs, and the same participant served as treated and control participant.
‡ Crossover design.
§ Based on average body weight or height presented in article.
‖ Range.
¶ Multiple dosages provided.
** Two participants were unable to complete exercise protocol while receiving growth hormone.
†† Each dose is an average of the range of published doses.
‡‡ Data from growth hormone and non–growth hormone groups aggregated.
§§ Male data/female data.
‖‖ Data obtained from reference 49.
¶¶ High-dose group.
*** Assumed height and body weight for male participants: 5 feet, 11 inches, and/or 75 kg; assumed body weight for female participants, 60 kg.
††† Presumed male.
‡‡‡ Assumed mean body weight, 65 kg.

Growth hormone dosing regimens varied considerably among the included studies (Table 1). The studies could be divided into 2 principal types: those that evaluated the physiologic effects of a single dose of growth hormone and those that assessed the effects of longer-term dosing regimens. Seven studies evaluated the use of a single dose of growth hormone. Of these, 3 studies provided growth hormone subcutaneously (35, 36, 38) and 4 studies provided growth hormone intravenously (34, 37, 39, 40). Twenty studies provided growth hormone for more than 1 day (mean treatment duration, 20 days [SD, 18]) (Table 1). All of these studies provided growth hormone subcutaneously. Only 3 studies evaluated growth hormone for longer than 30 days (44–47, 70), and no study evaluated its use for more than 3 months. The mean daily dose of growth hormone was 36 μg/kg (SD, 21) among the included studies.

## Study Quality

No study fulfilled all of the evaluated quality criteria, although 2 studies fulfilled 7 of 8 criteria (Table 2). No

*Table 1*—Continued

| Mean BMI (SD), kg/m² | | Mean Baseline $Vo_2max$ (SD), mL/kg per min | | Study Intervention | |
|---|---|---|---|---|---|
| Growth Hormone Group | Control Group | Growth Hormone Group | Control Group | Duration of Growth Hormone Therapy, d | Initial Growth Hormone Dosage, μg/kg per d |
| 23.6 (1.7) | 23.6 (1.7) | NA | NA | - | 3§ |
| 22.6 (1.7) | 22.6 (1.7) | 62.0 (2.8) | 62 (2.8) | - | 33§ |
| NA | NA | NA | NA | - | 10, 25, 50, 100¶ |
| 23.6 (2.4) | 23.6 (2.4) | 37.9 (8.7) | 37.9 (8.7) | - | 10 |
| 23.0 (1.3) | 23.0 (1.3) | 65.0 (2.6) | 65.0 (2.6) | - | 33§ |
| 23.2 (1.7) | 23.2 (1.7) | NA | NA | - | 5 |
| 23.0 (2.8) | 23.0 (2.8) | NA | NA | - | 5 |
| 22.5 (NA)§ | 22.1 (NA)§ | NA | NA | 7 | 67 |
| NA | NA | NA | NA | 42 | 17, 34¶†† |
| NA | NA | NA | NA | 42 | 30 |
| 23.1 (2.6) | 23.2 (3.9) | 42.8 (7.2) | 45.2 (7.2) | 28 | 33, 67¶ |
| 22.2 (7.6)/22.5 (2.2)§§‡ | 23.3 (5.8)/20.7 (7.2)§§‡ | 55.1 (7.2)¶¶ | 54.3 (6.3)¶¶ | 28 | 67 |
| 27.5 (3.0) | 28.0 (3.1) | 41.8 (9.8) | 44.8 (7.9) | 6 | 19 |
| NA | NA | NA | NA | 6 | 50‖¶¶*** |
| 22.2 (2.0) | 21.4 (1.6) | 60.1 (9.6) | 57.8 (7.2) | 14 | 28§ |
| 24.0 (NA) [23–26‖] | 25.0 (NA) [24–26‖] | 54.2 (NA) [50.1–60.0‖] | 53.4 (NA) [49.4–60.0] | 28 | 67 |
| NA | NA | NA | NA | 7 | 100 |
| 23–27‖‡‡ | 23–27‖‡‡ | NA | NA | 14 | 20 |
| NA | NA | NA | NA | 14 | 53¶¶ |
| 23 (NA) 19–24‖ | 23 (NA) 19–24‖ | NA | NA | 10 | 62§‡‡‡ |
| 22.7 (1.5) | 22.7 (1.5) | NA | NA | 14 | 67¶¶ |
| 22.8 (1.7) | 22.8 (1.7) | NA | NA | 14 | 26, 52§¶ |
| 22.6 (2.8) | 24.2 (3.6) | 57.0 (6.4) | 56.0 (6.0) | 7 | 50 |
| 22.5–27.0‖ | 22.5–27.0‖ | NA | NA | 10 | 33 |
| 21.6–26.3‖ | 21.6–26.3‖ | NA | NA | 4 | 33 |
| 23.5 (NA)§ | 23.5 (NA)§ | NA | NA | 84 | 40 |
| 22.9 (13.2) | 22.9 (13.2) | NA | NA | 14 | 2 |

study clearly documented adequate concealment of treatment allocation at study enrollment.

### Quantitative Data Synthesis

Many studies provided data on body composition and basal metabolism outcomes; however, limited data were available on strength and exercise capacity (**Appendix Table 2**, available at www.annals.org). Sixteen studies evaluated adverse events. We compared the incremental change from trial start to trial end between growth hormone–treated and non–growth hormone–treated groups to determine a summary effect size (weighted mean difference) for body composition and strength measures and compared trial-end data between groups to determine the weighted mean difference for basal metabolism outcomes.

### Effects of Growth Hormone on Body Composition

Lean body mass increased significantly in growth hormone–treated groups compared with groups not treated with growth hormone (increase in lean body mass, 2.1 kg [95% CI, 1.3 to 2.9 kg]) (**Table 3** and **Appendix Figure 1**, available at www.annals.org). The decrease in fat mass approached statistical significance (change in fat mass, −0.9 kg [CI, −1.8 to −0.0 kg]). Weight increased, although the difference was not statistically significant (change in weight, 0.3 kg [CI, −0.5 to 1.1 kg]).

### Effects of Growth Hormone on Strength Outcomes

Two studies evaluated change in strength (47, 70). These studies treated participants with growth hormone for 42 days (47) and 84 days (70), the longest treatment durations of all included studies. With 1-repetition maximum voluntary strength testing, growth hormone use did not improve biceps strength (change, −0.2 kg [CI, −1.5 to 1.1 kg]) or quadriceps strength (change, −0.1 kg [CI, −1.8 to 1.5 kg]) (**Table 3** and **Appendix Figure 2**, available at www.annals.org). One study evaluated 7 other muscle groups for change in maximum strength and assessed 4 measures of change in muscle circumference (70)—none of these changes significantly differed between growth hormone–treated and non–growth hormone–treated groups.

### Effect of Growth Hormone on Basal Metabolism

Daily basal metabolic rate was higher in growth hormone–treated participants than in those not treated with growth hormone (basal metabolic rate, 141 kcal/d [CI, 69 to 213 kcal/d]) (**Table 3** and **Appendix Figure 3**, available

*Table 2.* **Study Quality***

| Study, Year (Reference) | Trial Quality Measures | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Were Growth Hormone– and Non–Growth Hormone–Treated Participants Similar at Baseline? | Was a Placebo Offered? | Was Treatment Allocation Concealed? | Were Eligibility Criteria Specified? | Were Study Participants Blinded? | Were Clinicians Blinded? | Were Point Estimates and Variability Presented? | Was an Intention-to-Treat Analysis Performed? |
| **Single-dose growth hormone** | | | | | | | | |
| Gravhølt et al., 1999 (34) | ● | NA | NA | ○ | NA | NA | ● | ● |
| Hansen et al., 2005 (1 d) (35) | ● | ● | NA | ● | ● | ● | ● | ○ |
| Hashimoto et al., 2000 (36) | NA | ● | NA | ⊙ | ● | ● | ● | ● |
| Irving et al., 2004 (37) | ● | ○ | NA | ● | ○ | ○ | ● | ● |
| Lange et al., 2002 (38) | ● | ● | NA | ● | ● | ● | ● | ⊙ |
| Møller et al., 1990 (39) | ● | ● | NA | ⊙ | ● | ● | ● | ● |
| Napoli et al., 2003 (40) | ● | ● | NA | ⊙ | ● | ○ | ● | ● |
| **Multiple-dose growth hormone** | | | | | | | | |
| Brixen et al., 1990, 1992, 1995 (41–43) | ● | ● | NA | ⊙ | ● | ● | ● | ○ |
| Crist et al., 1988, 1990, 1991 (44–46) | ● | ● | NA | ⊙ | ● | ● | ● | ● |
| Deyssig et al., 1993 (47) | NA | ● | NA | ● | ● | ● | ● | ○ |
| Ehrnborg et al., 2005 (33, 48) | ● | ● | NA | ● | ● | ● | ● | ● |
| Giannoulis et al., 2005, 2002, 2000, 2000 (49–52) | ● | ● | NA | ● | ● | ● | ● | ⊙ |
| Graham et al., 2007 (72–74) | ⊙ | ○ | NA | ● | ○ | ○ | ● | ● |
| Hansen et al., 2001 (53) | ● | ○ | NA | ○ | ○ | ○ | ● | ● |
| Hansen et al., 2005 (32) | ● | ● | NA | ● | ● | ● | ● | ● |
| Healy et al., 2006, 2003 (54, 55) | ● | ● | NA | ● | ● | ● | ● | ○ |
| Horber et al., 1993, 1991 (31, 56) | NA | ● | NA | ● | ● | NA | ● | ● |
| Kniess et al., 2003 (57) | NA | ● | NA | ⊙ | ● | NA | ⊙ | NA |
| Møller et al., 1991 (58) | ● | ● | NA | ⊙ | ● | ● | ● | ● |
| Møller et al., 1992 (59) | ● | ● | NA | ⊙ | ● | ● | ● | NA |

*Table 2*—Continued

| Study, Year (Reference) | Trial Quality Measures | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Were Growth Hormone– and Non–Growth Hormone–Treated Participants Similar at Baseline? | Was a Placebo Offered? | Was Treatment Allocation Concealed? | Were Eligibility Criteria Specified? | Were Study Participants Blinded? | Were Clinicians Blinded? | Were Point Estimates and Variability Presented? | Was an Intention-to-Treat Analysis Performed? |
| Møller et al., 1993 (60) | ● | ● | NA | ⊙ | ● | ● | ● | ● |
| Møller et al., 1995, 1996 (61, 62) | ● | ● | NA | ○ | ● | ● | ● | ● |
| Wallace et al., 2001, 2001, 1999 (63–65) | ⊙ | ● | NA | ● | ● | ● | ● | ● |
| Wolthers et al., 1999, 1996, 1996 (66–68) | ● | ● | NA | ⊙ | ● | ● | ⊙ | ● |
| Wolthers et al., 1998 (69) | ● | ● | NA | ⊙ | ● | ● | ⊙ | ● |
| Yarasheski et al., 1992 (70) | NA | ● | NA | ⊙ | ● | ● | ● | ○ |
| Yuen et al., 2004 (71) | ● | ● | NA | ⊙ | ● | ● | ● | ● |

* The section on single-dose growth hormone includes studies that provided 1 dose of growth hormone therapy; the section on multiple-dose growth hormone includes studies that provided growth hormone for >1 day. In each section, references are arranged in alphabetical order. NA = not available/unclear; ○ = quality measure not fulfilled; ⊙ = quality measure partially fulfilled; ● = quality measure fulfilled.

at www.annals.org). Resting respiratory exchange ratio or respiratory quotient was lower in growth hormone–treated participants (−0.02 [CI, −0.03 to −0.01]; mean among all participants, 0.78 [SD, 0.03]), reflecting the preferential use of lipids rather than carbohydrates for fuel at rest during growth hormone therapy. Resting heart rate was also significantly higher in growth hormone–treated participants (3.8 beats/min [CI, 0.2 to 7.4 beats/min]).

### Effect of Growth Hormone on Exercise Capacity

Six studies measured exercise capacity outcomes (**Appendix Table 2**, available at www.annals.org). Given the variability in exercise interventions, we present a narrative summary rather than pooling their exercise capacity results. In growth hormone–treated participants compared with those not treated with growth hormone, lactate levels during exercise trended higher in all 3 studies evaluating this outcome, although this finding was statistically significantly higher in only 2 studies (**Table 4**). Exercising levels of plasma free fatty acids and glycerol were significantly increased in growth hormone–treated participants in all studies that evaluated these outcomes, reflecting the lipolytic properties of growth hormone. However, the exercising respiratory exchange ratio or respiratory quotient was not significantly different (35, 38, 72–74, 54, 55) in growth hormone–treated participants compared with that in those not treated with growth hormone. Exercising

*Table 3.* Summary Effect Sizes for Body Composition, Strength, and Basal Metabolism*

| Clinical Area and Clinical Outcome | Study Samples, n† | Weighted Mean Difference (95% CI)‡ |
|---|---|---|
| **Body composition** | | |
| Change in body weight | 9 | 0.3 kg (−0.5 to 1.1 kg) |
| Change in fat mass | 10 | −0.9 kg (−1.9 to −0.0 kg) |
| Change in lean body mass | 11 | 2.1 kg (1.3 to 2.9 kg)§ |
| **Strength** | | |
| Change in biceps 1RM | 2 | −0.2 kg (−1.5 to 1.1 kg) |
| Change in quadriceps 1RM | 2 | −0.1 kg (−1.8 to 1.5 kg) |
| **Basal metabolism** | | |
| End basal metabolic rate | 7 | 141 kcal/d (69 to 213 kcal/d)‖ |
| End resting respiratory exchange ratio or respiratory quotient | 7 | −0.02 (−0.03 to −0.01)‖ |
| End resting heart rate | 11 | 3.8 beats/min (0.2 to 7.4 beats/min)¶ |

* 1RM = 1 repetition maximum.
† Includes subsamples based on sex and dose.
‡ Growth hormone–treated group minus non–growth hormone–treated group. The weighted mean difference provides summary effect sizes in the same units as the outcome of interest. A positive value indicates that the weighted mean value in the growth hormone–treated group was higher than the value in the group not treated with growth hormone.
§ $P < 0.01$.
‖ $P < 0.001$.
¶ $I^2 > 50\%$; $P < 0.05$.

*Table 4.* **Qualitative Summary for Exercise Capacity***

| Clinical Outcome (during Exercise) in Study, Year (Reference) | Comparison of Values in Growth Hormone–Treated Group vs. Non–Growth Hormone–Treated Group | Published *P* Value (Comparison between Groups) |
|---|---|---|
| **Plasma lactate level** | | |
| Hansen et al., 2005 (1 d) (35) | + | <0.001 |
| Irving et al., 2004 (37)† | + | 0.07, 0.7–1.0 |
| Lange et al., 2002 (38) | + | <0.001 |
| **Heart rate** | | |
| Hansen et al., 2005 (1 d) (35) | + | <0.02 |
| Irving et al., 2004 (37)† | + | 0.12–1.0 |
| Lange et al., 2002 (38) | + | <0.001 |
| Ehrnborg et al., 2005 (33, 48) | + | 0.08 |
| **Plasma free fatty acid level** | | |
| Hansen et al., 2005 (1 d) (35) | + | <0.0 |
| Lange et al., 2002 (38) | + | <0.001 |
| Healy et al., 2006, 2003 (54, 55) | + | <0.05 |
| **Plasma glycerol level** | | |
| Hansen et al., 2005 (1 d) (35) | + | <0.01 |
| Lange et al., 2002 (38) | + | <0.001 |
| Healy et al., 2006, 2003 (54, 55) | + | <0.05 |
| **Respiratory exchange ratio or respiratory quotient** | | |
| Hansen et al., 2005 (1 d) (35) | = | 0.64 |
| Lange et al., 2002 (38) | = | >0.76 |
| Healy et al., 2006, 2003 (54, 55) | = | –‡ |
| Graham et al., 2007 (72–74) | – | >0.05‡ |
| **Bicycling speed** | | |
| Lange et al., 2002 (38) | + | 0.39 |
| Lange et al., 2002 (38) | – | 0.44 |
| **$\dot{V}O_2max$** | | |
| Ehrnborg et al., 2005 (33, 48) | + | 0.76, 1.0 |
| Graham et al., 2007 (72–74) | + | >0.05‡ |
| **Power output** | | |
| Ehrnborg et al., 2005 (33, 48) | + | 0.84 |
| **Energy expenditure** | | |
| Healy et al., 2006, 2003 (54, 55) | = | –‡ |
| **Maximum inspiratory pressure (nonexercising)** | | |
| Graham et al., 2007 (72–74) | + | <0.05 |

* + indicates that value in growth hormone–treated group seemed higher or consistently higher than that in the non–growth hormone–treated group; – indicates that value in growth hormone–treated group seemed lower or consistently lower than that in the non–growth hormone–treated group; = indicates that values in both groups seemed similar. $\dot{V}O_2max$ = maximum oxygen uptake.
† Comparison of control group with multiple growth hormone treatment groups.
‡ Comparison not reported to be significantly different between groups ($P > 0.05$) or $P$ value not reported.

heart rate was significantly increased in 2 of 4 studies that evaluated this outcome (35, 38). Maximum inspiratory pressure (at rest) increased in growth hormone–treated participants compared with those not treated with growth hormone in 1 study (72–74). Groups did not differ in bicycling speed, exercising energy expenditure, and power output (1 study each) (38, 54, 55). Similarly, $VO_2max$ was not significantly different between growth hormone–treated and non–growth hormone–treated groups (2 studies) (33, 48, 72–74).

## Safety of Growth Hormone

Growth hormone–treated participants reported higher rates of adverse events than those not treated with growth hormone (Table 5). The former group reported more soft tissue edema and fatigue than the latter group (44% vs. 1% and 35% vs. 0%, respectively). Growth hormone–treated participants also experienced arthralgias and carpal tunnel syndrome more often than did those not treated with growth hormone.

## Sensitivity Analyses

We recalculated summary effect sizes after removing each study per iteration. Removing the study by Wolthers and colleagues (66–68) resulted in a statistically significant increase in weight among growth hormone recipients. Removing 1 of 5 studies that evaluated fat mass (32, 33, 44–46, 48, 70, 72–74) or 1 of 4 studies that evaluated resting heart rate (33, 48, 53, 69, 72–74) resulted in nonsignificant differences between participants who received and those who did not receive growth hormone. The results of other clinical outcomes were robust to this analysis.

We found little evidence for statistical heterogeneity among the included studies for body composition, strength outcomes, resting respiratory exchange ratio or respiratory quotient, and resting energy expenditure (**Appendix Figures 1 to 3**, available at www.annals.org). However, the summary results for resting heart rate were statistically heterogeneous ($P$ for $Q$ statistic = 0.01; $I^2$ = 55%) (Table 3). Part of this heterogeneity could be explained by duration of growth hormone treatment. When we recalculated the resting heart rate from studies that provided growth hormone for at least 14 days, we found no evidence for heterogeneity ($P$ for $Q$ statistic = 0.26; $I^2$ = 22%). We found little evidence of publication bias through visual inspection of funnel plots.

# Discussion

Growth hormone is reported to be extensively used for illicit enhancement of athletic performance (5, 8, 75), both for its anabolic and endurance effects. However, our review of the limited published literature suggests that although growth hormone may alter body composition, it has minimal effect on key athletic performance outcomes and may, in fact, be associated with worsened exercise capacity. Our conclusions are consistent with the findings reported in the recent Mitchell report on illegal drug use in Major League Baseball, which noted the lack of evidence supporting growth hormone use and enhancement of athletic performance (10).

*Table 5.* Key Adverse Events

| Adverse Event* | Studies Reporting Outcome, *n* | Events in Growth Hormone–Treated Group, *n (%)* | Events in Non–Growth Hormone–Treated Group, *n (%)* |
|---|---|---|---|
| Soft tissue edema | 8 | 33 (44) | 1 (1) |
| Fatigue | 4 | 11 (35) | 0 (0) |
| Arthralgias | 2 | 4 (25) | 0 (0) |
| Carpal tunnel syndrome | 2 | 3 (15) | 0 (0) |
| Sweating | 1 | 3 (30) | 2 (20) |

* Participants may have reported more than 1 adverse event.

Athletes, in particular bodybuilders, reportedly use growth hormone to increase strength and improve muscle definition (5, 17, 76). We found that although growth hormone significantly increased lean body mass and was associated with a near-significant trend toward decreased fat mass, it did not result in gains in biceps and quadriceps strength. How can increases in lean body mass not translate into strength improvements? Because methods for evaluation of lean body mass do not reliably distinguish lean solid tissue from fluid mass (77) and because the included studies evaluated only short-term changes, we suspect that much of the increase in lean body mass from growth hormone is due to fluid retention rather than muscle hypertrophy (77–79). A nonrandomized study in experienced weightlifters supports this view. Yarasheski and colleagues (80) provided high-dose growth hormone to college football players and weightlifters and found that it did not increase muscle protein synthesis or decrease protein breakdown, suggesting that an increase in muscle mass from growth hormone use in such athletes is unlikely.

We found that growth hormone did not improve and, in fact, may worsen exercise capacity. Exercising lactate levels were significantly higher in growth hormone–treated participants than in non–growth hormone–treated participants in 2 of 3 studies that evaluated this outcome. Increased exercising lactate levels are associated with decreased exercise stamina and physical exhaustion (81). In the double-blind study by Lange and colleagues (38), 2 of 7 cyclists could complete the exercise protocol after receiving placebo but not growth hormone; this finding was replicated on repeated testing in 1 cyclist. It is not clear how growth hormone treatment increases exercising lactate levels, but it may be associated with increased action of uncoupling proteins in mitochondria or selective inhibition of pyruvate dehydrogenase (38). In addition, elevated glycerol concentrations observed during the growth hormone trials could provide an alternate gluconeogenic precursor, thus increasing blood lactate levels by reducing lactate clearance by the liver. However, our exercise capacity results must be interpreted with caution because all 3 studies evaluated exercising lactate levels after only 1 dose of growth hormone, a dosing protocol unlikely to mirror real-world regimens. Nonetheless, this finding merits further research because it suggests that endurance athletes who use growth hormone may actually be harming their athletic performance.

One recent study (72–74) included in our analysis reported respiratory function improvements (including maximum inspiratory and expiratory pressures) in participants treated with growth hormone compared with those not treated with growth hormone, although $VO_2$max was not reported to statistically significantly differ. Whether these findings translate into improved athletic performance is unclear. In healthy people at sea level, pulmonary function is typically not considered to be limiting to performance (82). Even during maximal exercise, participants could increase ventilation (82), suggesting an existing ventilatory reserve. Additional studies evaluating the effects of pulmonary function change on athletic performance are needed to evaluate these authors' findings.

While growth hormone therapy resulted in increased use of lipids for fuel during rest (as noted by a statistically significantly lower resting respiratory exchange ratio and respiratory quotient), this improvement did not seem to persist during exercise. Although growth hormone therapy resulted in higher exercising serum free fatty acid and glycerol levels, exercising respiratory exchange ratio and respiratory quotient levels were not reported to significantly differ in growth hormone–treated versus non–growth hormone–treated participants. Free fatty acid availability can affect free fatty acid uptake at rest and during low-intensity exercise, but exercise intensity remains the predominant determinant of substrate selection and can override other influences, especially at high rates of work output. As is the case after endurance training, a lower respiratory exchange ratio and respiratory quotient, signifying increased lipid rather than carbohydrate oxidation, are thought to contribute to improved exercise endurance due to glycogen preservation (83). The observation that respiratory exchange decrements with growth hormone did not persist during exercise suggests that short-term growth hormone treatment may not enhance endurance, at least through a mechanism of altered substrate selection. This conclusion cannot be considered definitive given the small number of included studies, but it suggests that additional research is needed to further delineate growth hormone's effects on endurance.

We found higher rates of adverse events in growth hormone–treated participants than in non–growth hormone–treated participants. Consistent with studies in growth hormone–deficient patients (84, 85) and healthy elderly participants (20), we found higher proportions of soft tissue edema, joint pain, and carpal tunnel syndrome in participants receiving growth hormone, although variability in reporting adverse events precluded us from performing statistical analyses on these results. Adverse events related to fluid retention have been well described in growth hormone–treated patients (86, 87) and are thought to be due to growth hormone's effect on fluid homeostasis. Of note, growth hormone–treated participants reported higher rates of fatigue, consistent with our finding that growth hormone may in fact worsen exercise capacity.

Our study reflects the limitations of the included studies. First, our review highlights the lack of published evidence about the physiologic effects of growth hormone among athletic young adults. Although we reviewed thousands of studies, only 8 studies assessed strength and exercise capacity for growth hormone treatment in a randomized manner. Thus, our analysis may not have detected small but clinically relevant differences in outcomes and adverse events. Because no studies evaluated growth hormone for longer than 3 months, there is no evidence with which to evaluate the long-term use of growth hormone for athletic enhancement. In addition, because only a small percentage of participants were women, there is almost no evidence with which to evaluate the effect of growth hormone in physically fit young women. Second, published data on real-world doping regimens are limited, and growth hormone dosing regimens used in research settings may be lower than or otherwise differ from those used by athletes who engage in sports doping. Saugy and colleagues (75) reported that athletes may be using growth hormone in dosages ranging from approximately 15 to 180 μg/kg per day (75), which may be higher than dosages used in most of our included studies. Whether a graded dose response exists for growth hormone is unclear (15), and future research should evaluate growth hormone regimens used in real-world settings. Finally, anecdotal reports of sports doping regimens suggest that growth hormone is not typically used as a single agent (5), but rather is often combined with other drugs, including androgenic steroids, insulin, and antiestrogens (76). Real-world sports doping regimens may have different benefits and risks from those noted in our analyses.

Claims regarding the performance-enhancing properties of growth hormone are premature and are not supported by our review of the literature. The limited published data evaluating the effects of growth hormone on athletic performance suggest that although growth hormone increases lean body mass in the short term, it does not seem to improve strength and may worsen exercise capacity. In addition, growth hormone use in healthy young persons is frequently associated with adverse events. More research, including an identification and evaluation of real-world growth hormone doping protocols, is warranted to definitively determine the effects of growth hormone on athletic performance.

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| *Appendix Table 1.* Search Strategy* | | |
|---|---|---|
| **Search Number (Date)** | **Search Terms** | **Articles Returned, *n*** |
| **MEDLINE** | | |
| (31 August 2006) | | |
| 1 | ("Growth Hormone"[MeSH] OR growth hormone*[tw]) | 53 732 |
| 2 | ("Adult"[MeSH] OR "Adolescent"[MeSH]) | 4 143 448 |
| 3 | (randomized controlled trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR random allocat*[tw] OR randomly allocat*[tw] OR double-blind method [mh] OR single-blind method [mh] OR double blind*[tw] OR single blind*[tw] OR triple blind*[tw] OR clinical trial [pt] OR clinical trials [mh]) NOT (animal[mh] NOT human[mh]) | 591 966 |
| 4 | "Middle Aged"[MeSH] OR "Aged"[MeSH] | 2 585 607 |
| 5 | "Child"[MeSH] OR "Child, Preschool"[MeSH] OR "Infant"[MeSH] OR "Infant, Newborn"[MeSH] | 1 510 685 |
| 6 | #1 AND #2 AND #3 | 3382 |
| 7 | #1 AND #3 | 4202 |
| 8 | #7 NOT #6 | 820 |
| 9 | #1 AND #3 AND #4 | 1552 |
| 10 | #1 AND #3 AND #5 | 1013 |
| 11 | #8 NOT #9 | 820 |
| 12 | #8 NOT #10 | 387 |
| 13 | #8 NOT (#9 OR #10) | 387 |
| 14 | #8 NOT #13 | 433 |
| Updated: 7 September 2006 | | |
| 1 | ("Growth Hormone"[MeSH] OR growth hormone*[tw]) | 53 755 |
| 2 | (randomized controlled trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR random allocat*[tw] OR randomly allocat*[tw] OR double-blind method [mh] OR single-blind method [mh] OR double blind*[tw] OR single blind*[tw] OR triple blind*[tw] OR clinical trial [pt] OR clinical trials [mh]) NOT (animal[mh] NOT human[mh]) | 592 629 |
| 3 | #1 AND #2 Limits: Entrez Date from 2006/07/13 [to present] | 7 |
| Summary | Total titles identified from MEDLINE search | 4180 |
| Updated: 11 October 2007 | | |
| | Additional studies identified from MEDLINE search | 286 |
| Summary | Total titles identified from MEDLINE search | 4466 |
| **EMBASE** | | |
| (7 September 2006) | | |
| S1 | Human Growth Hormone! OR growth hormone! OR growth hormone? | 89 040 |
| S3 | randomi?(W)controlled(W)trial? OR DT=randomized controlled trial | 385 891 |
| S4 | random?(W)alloc? OR random allocation! OR double(W)Blind? OR single(W)blind? | 284 456 |
| S5 | trip?(W)blind? OR clinical trials! OR clinical trial! OR DT=clinical trial | 948 086 |
| S6 | S3 OR S4 OR S5 | 1 064 129 |
| S7 | S6 AND S1 | 7634 |
| S8 | S (LT = animal or animals/df) NOT (humans/df OR human/df) | 6 094 879 |
| S9 | S7 NOT S8 | 7245 |
| S10 | RD S9 Unique Embase records | 2325 |
| Updated: 11 October 2007 | | |
| | Additional studies identified from EMBASE search | 420 |
| Summary | Total titles identified from EMBASE search | 2745 |
| **SPORTDiscus** | | |
| (7 September 2006) | | |
| 1 | exp somatotropin/ | 725 |
| 2 | growth hormone$.mp. | 711 |
| 3 | 1 or 2 | 953 |
| 4 | limit 3 to (article or book analytic or "book review" or microform or monograph or serial publication or "thesis or dissertation" or url) | 953 |
| 5 | exp ANIMAL/ | 10 028 |
| 6 | 4 not 5 | 925 |
| 7 | 4 not 6 | 28 |
| 8 | exp clinical trial/ | 1084 |
| 9 | double-blind method/ | 0 |
| 10 | random$ controlled trial$.mp | 976 |
| 11 | double blind$.mp. | 732 |
| 12 | single blind$.mp. | 91 |
| 9 | double-blind method/ | 0 |
| 10 | random$ controlled trial$.mp | 976 |
| 11 | double blind$.mp. | 732 |

*Continued on following page*

*Appendix Table 1*—**Continued**

| Search Number (Date) | Search Terms | Articles Returned, n |
|---|---|---|
| 12 | single blind$.mp. | 91 |
| 13 | triple blind$.mp | 1 |
| 14 | random$ alloc$.mp | 82 |
| 15 | 8 or 9 or 10 or 11 or 12 or 13 or 14 | 1979 |
| 16 | 3 and 15 | 23 |
| | Unique titles (2 eliminated, identified in prior search) | 21 |
| Updated: 11 October 2007 | | |
| | Additional studies identified from SPORTDiscus search | 23 |
| Summary | Total titles identified from SPORTDiscus search | 44 |
| **Cochrane Collaboration** (7 September 2006) | | |
| 1 | growth hormone$.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] | 3422 |
| | EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2006> (3371) | |
| | EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2006> (36) | |
| | EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2006> (15) | |
| 2 | limit 2 to medline records [Limit not valid in: CDSR,DARE; records were retained] | 2642 |
| | EBM Reviews Cochrane Central Register of Controlled Trials <3rd Quarter 2006> (2591) | |
| | EBM Reviews Cochrane Database of Systematic Reviews <3rd Quarter 2006> (36) | |
| | EBM Reviews Database of Abstracts of Reviews of Effects <3rd Quarter 2006> (15) | |
| 3 | 1 not 2 | 780 |
| 4 | limit 3 to Embase records [Limit not valid in: CDSR,DARE; records were retained] | 503 |
| 5 | 3 not 4 | 328 |
| | EBM Reviews Cochrane Central Register of Controlled Trials <3rd Quarter 2006> (328) | |
| | EBM Reviews Cochrane Database of Systematic Reviews <3rd Quarter 2006> (0) | |
| | EBM Reviews Database of Abstracts of Reviews of Effects <3rd Quarter 2006> (0) | |
| Updated: 11 October 2007 | | |
| | Additional studies identified from Cochrane Collaboration search | 26 |
| Summary | Total titles identified from Cochrane Collaboration search | 344 |

* Searches current through 11 October 2007.

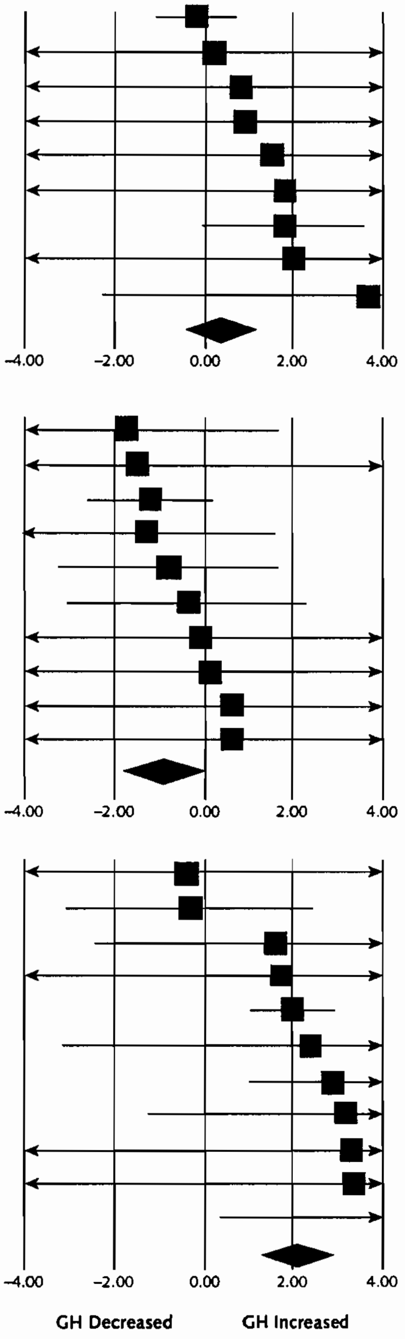
*Appendix Table 2.* Key Outcomes Available for Analysis*

| Study, Year (Reference) | Body Composition | | | Strength Outcomes | | Basal Metabolism (Nonexercising) | | | Exercise Capacity (Exercising) | | | | | | | | | Adverse Events Reported |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Body Weight | LBM or FFM | FM | Biceps 1RM | Quadriceps 1RM | EE or BMR | Heart Rate | RER or RQ | Heart Rate | Lactate Level | FFA or Glycerol | RER or RQ | $\dot{V}o_2$ max | Power Output | Cycling Speed | EE | MIP (Nonexercising) | |
| **Single-dose growth hormone** | | | | | | | | | | | | | | | | | | |
| Gravhølt et al., 1999 (34) | | | | | | √ | | √ | | | | | | | | | | |
| Hansen et al., 2005 (1 d) (35) | | | | | | | | | √ | √ | √ | √ | | | | | | √ |
| Hashimoto et al., 2000 (36) | | | | | | | | | | | | | | | | | | √ |
| Irving et al., 2004 (37) | | | | | | | | | √ | √ | | | | | | | | |
| Lange et al., 2002 (38) | | | | | | | | | √ | √ | √ | √ | | | √† | | | √ |
| Møller et al., 1990 (39) | | | | | | √ | | √ | | | | | | | | | | |
| Napoli et al., 2003 (40) | | | | | | | √ | | | | | | | | | | | |
| **Multiple-dose growth hormone** | | | | | | | | | | | | | | | | | | |
| Brixen et al., 1990, 1992, 1995 (41–43) | √ | | | | | | | | | | | | | | | | | √ |
| Crist et al., 1988, 1990, 1991 (44–46) | | √† | √† | | | | | | | | | | | | | | | √ |
| Deyssig et al., 1993 (47) | | √ | √ | √ | √ | | | | | | | | | | | | | √ |
| Ehrnborg et al., 2005 (33, 48) | √‡ | √‡ | √‡ | | | | √‡ | | √ | | | | √ | √ | | | | √ |
| Giannoulis et al., 2005, 2002, 2000, 2000 (49–52) | | | | | | | √†§ | | | | | | | | | | | √† |
| Graham et al., 2007 (72–74) | √ | | √ | | | | √ | | | | | √ | √ | | | | √ | √ |
| Hansen et al., 2001 (53) | | | | | | | √ | | | | | | | | | | | |
| Hansen et al., 2005 (32) | √ | √ | √ | | | √ | | | | | | | | | | | | √ |
| Healy et al., 2006, 2003 (54, 55) | √ | √ | √ | | | | | √ | | | √ | √ | | | | √ | | √ |
| Horber et al., 1993, 1991 (31, 56) | | | | | | √ | | √ | | | | | | | | | | |
| Kniess et al., 2003 (57) | | | | | | | | | | | | | | | | | | √ |
| Møller et al., 1991 (58) | | | | | | | | | | | | | | | | | | √ |
| Møller et al., 1992 (59) | | | | | | | | √ | | | | | | | | | | √ |
| Møller et al., 1993 (60) | | | | | | √ | | √ | | | | | | | | | | |
| Møller et al., 1995 (61, 62) | | | | | | | √† | | | | | | | | | | | |
| Wallace et al., 2001, 2001, 1999 (63–65) | | | | | | | | | | | | | | | | | | √ |
| Wolthers et al., 1999, 1996, 1996 (66–68) | √ | √ | | | | √ | | | | | | | | | | | | |
| Wolthers et al., 1998 (69) | | √ | | | | √ | √ | √ | | | | | | | | | | |
| Yarasheski et al., 1992 (70) | √ | √ | √ | √ | √ | | | | | | | | | | | | | √ |
| Yuen et al., 2004 (71) | √ | √ | √ | | | | √ | | | | | | | | | | | |

* Upper section includes studies that provided 1 dose of growth hormone therapy; lower section includes studies that provided growth hormone for >1 day. In each section, references are arranged in alphabetical order. Check mark indicates that data were available for and are included in analysis. 1RM = 1 repetition maximum; BMR = basal metabolic rate; EE = energy expenditure; FFA = free fatty acids; FFM = fat-free mass; FM = fat mass; LBM = lean body mass; MIP = maximum inspiratory pressure; RER = respiratory exchange rate; RQ = respiratory quotient; $\dot{V}o_2$max = maximum oxygen uptake.
† Includes separate data for low-dose and high-dose growth hormone treatment.
‡ Includes separate data for men and women.
§ Data obtained from reference 50.

*Appendix Figure 1.* **Effect of growth hormone (*GH*) on body composition.**

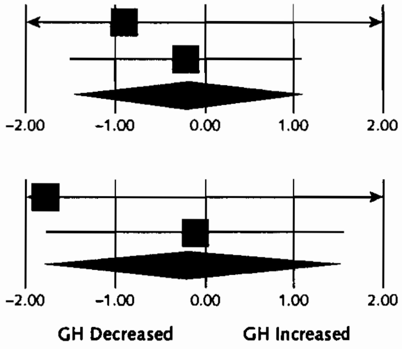
| Study (Reference) | Difference in Means | Lower Limit | Upper Limit | *P* Value | GH Group | Control Group |
|---|---|---|---|---|---|---|
| **Weight, *kg*** | | | | | | |
| Wolthers et al. (66–68) | –0.190 | –1.120 | 0.740 | 0.689 | 8 | 8 |
| Yuen et al. (71) | 0.200 | –9.043 | 9.443 | 0.966 | 12 | 12 |
| Graham et al. (72–74) | 0.800 | –5.451 | 7.051 | 0.802 | 24 | 24 |
| Hansen et al. (32) | 0.900 | –6.311 | 8.111 | 0.807 | 8 | 8 |
| Ehrnborg et al. (33, 48)* | 1.500 | –8.473 | 11.473 | 0.768 | 10 | 5 |
| Brixen et al. (41–43) | 1.800 | –4.080 | 7.680 | 0.549 | 10 | 10 |
| Yarasheski et al. (70) | 1.800 | –0.074 | 3.674 | 0.060 | 7 | 9 |
| Ehrnborg et al. (33, 48)† | 2.000 | –6.134 | 10.134 | 0.630 | 10 | 5 |
| Healy et al. (54, 55) | 3.700 | –2.310 | 9.710 | 0.228 | 6 | 5 |
| Total | 0.337 | –0.458 | 1.133 | 0.406 | 95 | 86 |
| **Fat mass, *kg*** | | | | | | |
| Crist et al. (44–46)‡ | –1.770 | –5.206 | 1.666 | 0.313 | 8 | 8 |
| Ehrnborg et al. (33, 48)* | –1.500 | –7.945 | 4.945 | 0.648 | 10 | 5 |
| Yarasheski et al. (70) | –1.200 | –2.609 | 0.209 | 0.095 | 7 | 9 |
| Hansen et al. (32) | –1.200 | –4.088 | 1.688 | 0.415 | 8 | 8 |
| Graham et al. (72–74) | –0.800 | –3.291 | 1.691 | 0.529 | 24 | 24 |
| Crist et al. (44–46)§ | –0.350 | –3.045 | 2.345 | 0.799 | 8 | 8 |
| Healy et al. (54, 55) | –0.100 | –4.471 | 4.271 | 0.964 | 6 | 5 |
| Deyssig et al. (47) | 0.110 | –5.468 | 5.688 | 0.969 | 8 | 10 |
| Yuen et al. (71) | 0.600 | –8.242 | 9.442 | 0.894 | 12 | 12 |
| Ehrnborg et al. (33, 48)† | 0.600 | –4.448 | 5.648 | 0.816 | 10 | 5 |
| Total | –0.927 | –1.852 | –0.001 | 0.050 | 101 | 94 |
| **Lean body mass, *kg*** | | | | | | |
| Yuen et al. (71) | –0.400 | –9.242 | 8.442 | 0.929 | 12 | 12 |
| Wolthers et al. (69) | –0.300 | –3.086 | 2.486 | 0.833 | 8 | 8 |
| Ehrnborg et al. (33, 48)† | 1.600 | –2.449 | 5.649 | 0.439 | 10 | 5 |
| Crist et al. (44–46)§ | 1.730 | –8.628 | 12.088 | 0.743 | 8 | 8 |
| Wolthers et al. (66–68) | 2.000 | 1.020 | 2.980 | 0.000 | 8 | 8 |
| Hansen et al. (32) | 2.400 | –3.207 | 8.007 | 0.402 | 8 | 8 |
| Yarasheski et al. (70) | 2.900 | 1.026 | 4.774 | 0.002 | 7 | 9 |
| Healy et al. (54, 55) | 3.200 | –1.263 | 7.663 | 0.160 | 6 | 5 |
| Crist et al. (44–46)‡ | 3.330 | –7.254 | 13.914 | 0.537 | 8 | 8 |
| Ehrnborg et al. (33, 48)* | 3.400 | 4.933 | 11.733 | 0.424 | 10 | 5 |
| Deyssig et al. (47) | 4.100 | 0.358 | 7.842 | 0.032 | 8 | 10 |
| Total | 2.092 | 1.328 | 2.855 | 0.000 | 93 | 86 |



We used a random-effects model and a weighted mean difference effect size to compare GH-treated and non–GH-treated participants. The black diamond represents the summary effect size for the outcome of interest. Values greater than 0 indicate that results with GH treatment were higher than those without GH treatment. The studies are ordered by mean effect size. *Male. †Female. ‡High-dose group. §Low-dose group.

**Appendix Figure 2.** Effect of growth hormone (*GH*) on strength.

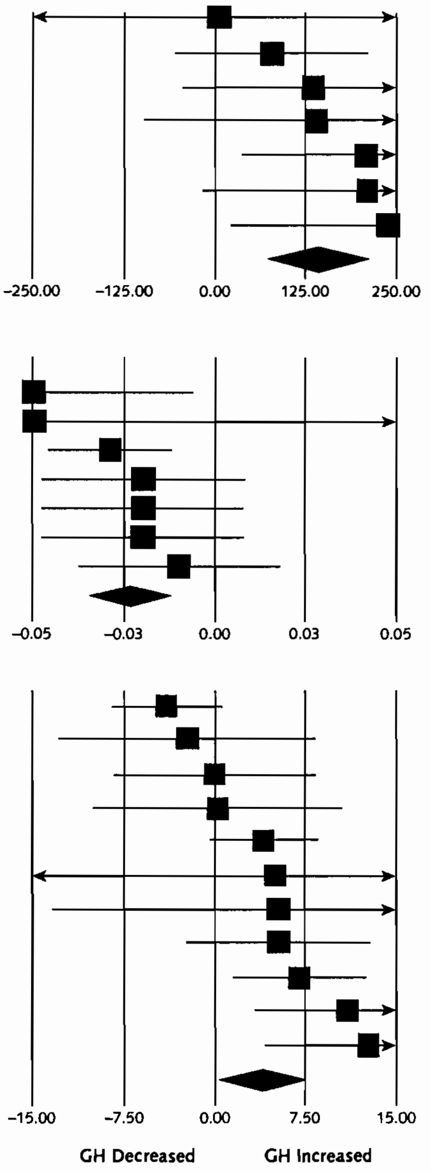
| Study (Reference) | Difference in Means | Lower Limit | Upper Limit | *P* Value | GH Group | Control Group |
|---|---|---|---|---|---|---|
| Biceps 1RM, *kg* | | | | | | |
| Deyssig et al. (47) | −0.900 | −13.554 | 11.754 | 0.889 | 11 | 11 |
| Yarasheski et al. (70) | −0.200 | −1.515 | 1.115 | 0.766 | 9 | 9 |
| Total | −0.207 | −1.515 | 1.100 | 0.756 | 20 | 20 |
| Quadriceps 1RM, *kg* | | | | | | |
| Deyssig et al. (47) | −1.800 | −14.114 | 10.514 | 0.774 | 11 | 11 |
| Yarasheski et al. (70) | −0.100 | −1.786 | 1.586 | 0.907 | 9 | 9 |
| Total | −0.131 | −1.802 | 1.539 | 0.878 | 20 | 20 |



We used a random-effects model and a weighted mean difference effect size to compare GH-treated and non–GH-treated participants. The black diamond represents the summary effect size for the outcome of interest. Values greater than 0 indicate that results with GH treatment were higher than those without GH treatment. The studies are ordered by mean effect size. 1RM = 1 repetition maximum.

*Appendix Figure 3.* **Effect of growth hormone (*GH*) on basal metabolism.**

| Study (Reference) | Difference in Means | Lower Limit | Upper Limit | *P* Value | GH Group | Control Group |
|---|---|---|---|---|---|---|
| **Basal metabolic rate, *kcal/d*** | | | | | | |
| Møller et al. (39) | 7.000 | −250.472 | 264.472 | 0.958 | 6 | 6 |
| Gravhølt et al. (34) | 79.000 | −55.497 | 213.497 | 0.250 | 8 | 8 |
| Wolthers et al. (69) | 135.000 | −45.508 | 315.508 | 0.143 | 8 | 8 |
| Horber et al. (31, 56) | 141.000 | −99.246 | 381.246 | 0.250 | 8 | 8 |
| Wolthers et al. (66–68) | 209.000 | 36.056 | 381.944 | 0.018 | 8 | 8 |
| Møller et al. (60) | 210.000 | −18.569 | 438.569 | 0.072 | 6 | 6 |
| Hansen et al. (32) | 239.000 | 19.589 | 458.411 | 0.033 | 8 | 8 |
| Total | 140.984 | 68.765 | 213.204 | 0.000 | 52 | 52 |
| **Resting RER or RQ** | | | | | | |
| Møller et al. (60) | −0.050 | −0.094 | −0.006 | 0.025 | 6 | 6 |
| Møller et al. (59) | −0.500 | −0.191 | 0.091 | 0.488 | 14 | 14 |
| Møller et al. (39) | −0.029 | −0.046 | −0.012 | 0.001 | 6 | 6 |
| Healy et al. (54, 55) | −0.020 | −0.048 | 0.008 | 0.161 | 6 | 5 |
| Wolthers et al. (69) | −0.020 | −0.048 | 0.008 | 0.157 | 8 | 8 |
| Gravhølt et al. (34) | −0.020 | −0.048 | 0.008 | 0.157 | 8 | 8 |
| Horber et al. (31, 56) | −0.010 | −0.038 | 0.018 | 0.480 | 8 | 8 |
| Total | −0.024 | −0.034 | −0.013 | 0.000 | 56 | 55 |
| **Resting heart rate, *beats/min*** | | | | | | |
| Giannoulis et al. (49–52)*† | −4.000 | −8.569 | 0.569 | 0.086 | 17 | 25 |
| Ehrnborg et al. (33, 48)* | −2.300 | −12.895 | 8.295 | 0.671 | 10 | 10 |
| Napoli et al. (40) | 0.000 | −8.315 | 8.315 | 1.000 | 8 | 8 |
| Yuen et al. (71) | 0.200 | −10.125 | 10.525 | 0.970 | 12 | 12 |
| Giannoulis et al. (49–52)†‡ | 4.000 | −0.538 | 8.538 | 0.084 | 18 | 25 |
| Møller et al. (61, 62)* | 5.000 | −19.811 | 29.811 | 0.693 | 8 | 8 |
| Møller et al. (61, 62)‡ | 5.300 | −13.410 | 24.010 | 0.579 | 8 | 8 |
| Ehrnborg et al. (33, 48)‡ | 5.300 | −2.385 | 12.985 | 0.176 | 10 | 10 |
| Wolthers et al. (69) | 7.000 | 1.456 | 12.544 | 0.013 | 8 | 8 |
| Graham et al. (72–74) | 11.000 | 3.232 | 18.768 | 0.006 | 24 | 24 |
| Hansen et al. (53) | 13.000 | 4.091 | 21.909 | 0.004 | 8 | 8 |
| Total | 3.806 | 0.213 | 7.398 | 0.038 | 131 | 146 |



We used a random-effects model and a weighted mean difference effect size to compare GH-treated and non–GH-treated participants. The black diamonds represents the summary effect size for the outcome of interest. Values greater than 0 indicate that results with GH treatment were higher than those without GH treatment. The studies are ordered by mean effect size. RER = respiratory exchange rate; RQ = respiratory quotient. *Low-dose group; data obtained from reference 50. †Low-dose GH. ‡High-dose GH. Data obtained from reference 50. §High-dose GH.